ENANTIOSELECTIVE TOTAL SYNTHESIS OF CYATHIN A_3

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in the Department of Chemistry
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by

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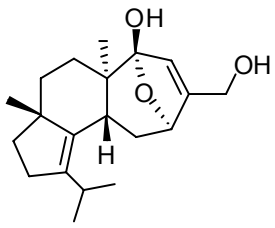
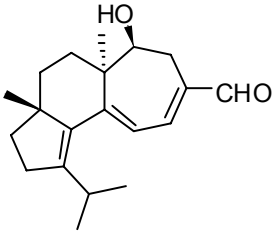
Abstract

The cyathins are a unique group of diterpenoids produced by the bird's nest fungi *Cyathus helenae*, *C. africanus, and C. earlei*. Several of the cyathins show strong antibiotic activity. More recently, several fungal metabolites with structures closely related to those of the cyathins have been found to be potent inducers of nerve growth factor (NGF) synthesis. The structural complexity and the exciting biological activity of the cyathane family of diterpenes have prompted our efforts to develop an efficient and general synthetic approach.



cyathin A_3

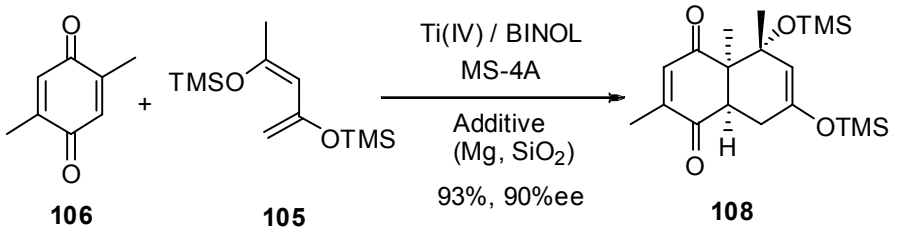


allocyathin B_2

To date, there have been seven total syntheses and six partial syntheses of cyathins. Most of these syntheses target allocyathin B_2, which does not contain the common 6-7 *trans* ring fusion or the hydroxyl group within the seven member ring. Modifications of these routes to provide targets with these features have not been demonstrated and may be challenging. We have developed a concise asymmetric synthesis of cyathin A_3, based on the enantioselective Diels-Alder reaction of quinone (**106**) and diene (**105**). Because the transformations of cyathin A_3 into other cyathins are well documented, this synthesis provides a general approach to the cyathane diterpene family.

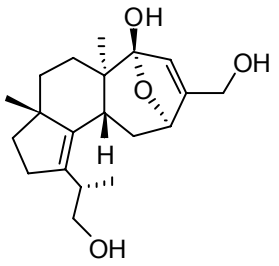
In Section 2.2, the enantioselective Diels-Alder reaction of quinone **106** and diene **105** is presented. This reaction is effectively catalyzed by a carefully

prepared Mikami catalyst. It was carried out on a preparative scale to give the chiral building block **108**. The absolute configuration of the Diels-Alder adduct **108** was determined by NMR and X-ray analysis.

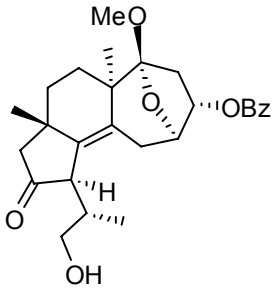


106 **105** **108**

In Sections 2.3-5, the enantioselective total synthesis of (-)-cyathin A_3 is described. This approach features the successful oxymercuration ring opening, a newly developed *in situ* configuration inversion, a much improved intramolecular aldol reaction and a radical cyclization. Now envisioned in our laboratory is the development of a new access to cyathin A_4 (**5**), which is surmised to be possible via the intermediate prepared in this synthesis (e.g., **128**).



5 cyathin A_4



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With much love and appreciation I thank my father Shaoliu, and my mother Y. Wang for their loving support and enthusiasm.

With much love and appreciation I thank my wife Yunhua. I would not have been able to accomplish what I have today without her love and encouragement.

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List of Schemes

List of abbreviations

Ac	acetyl (ethanoyl)
Ac_2O	acetic anhydride
AcCl	acetyl chloride
AcOH	acetic acid
aq	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
^{13}C NMR	carbon-13 nuclear magnetic resonance
Cbz	benzyloxycarbonyl
Chx	cyclohexyl
CI	chemical ionization
CSA	camphorsulfonic acid
DA	Diels-Alder
DABCO	1,4-diazabicyclo[2.2.2]octane
DCC	1,3-dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate; $EtO_2C\text{-}N{=}N\text{-}CO_2Et$
DET	diethyl tartrate
DIBAL	diisobutylaluminium hydride
dil.	dilute
DIPEA	diisopropylethylamine

DIPT	diisopropyl tartrate
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	dimethylformamide
DMP	2,2-dimethoxypropane
DMS	dimethylsulphide
DMSO	methyl sulphoxide
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dr	diastereomers ratio
DRIFT	diffuse reflectance Fourier transform infrared
ee	enantiomeric excess; for a mixture of two enantiomers *R* and *S*, ee=|([*R*]-[*S*])|/([*R*]+[*S*]) x 100%
EI	electron impact ionization
equiv	equivalent(s)
er	enantiomeric ratio; ratio of (*R*) to (*S*)
Et	ethyl
Et_2O	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate
FAB	fast-atom bombardment
FCC	flash column chromatography
FID	free induction decay (in NMR spectroscopy)
FTIR	Fourier transform infrared
^1H NMR	proton nuclear magnetic resonance
h	hour(s)
H-bonding	hydrogen bonding

HMBC	heteronuclear multiple bond correlation (2 and 3 bond J_{CH} correlation with inverse detection)
HMQC	heteronuclear multiple quantum coherence (1 bond J_{CH} correlation with inverse detection)
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
i-Bu	isobutyl (2-methylpropyl)
i-Pr	isopropyl
IR	infrared
LA	Lewis Acid
LB	Lewis Base
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrometry
m-CPBA	3-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeLi	methyllithium
MHz	megahertz; 10^6 Hertz
min	minute(s)
MOM	methoxymethyl
MPC	medium pressure chromatography
MPM or PMB	*p*-methoxybenzyl or *p*-methoxyphenylmethyl
MS	mass spectrometry
MS4A	molecular sieves 4Å
MsCl	methanesulphonyl chloride

MTPA	2-methoxy-2-(trifluoromethyl)-2-phenylacetic acid
MTPACl	2-methoxy-2-(trifluoromethyl)-2-phenylacetyl chloride
na	not applicable
NBS	N-bromosuccinimide
n-BuLi	*n*-butyllithium
nd	not determined
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement
NR	no reaction
OTBDMS	*tert*-butyldimethylsilyloxy
OTf	trifluoromethanesulfonyloxy (CF_3SO_2O)
PMB or MPM	*p*-methoxybenzyl or *p*-methoxyphenylmethyl
PTLC	preparative thin layer chromatography
p-TsOH	*p*-toluenesulfonic acid (4-methylbenzenesulfonic acid)
Pyr	pyridine
rs	regioselectivity (mole fraction of the major regioisomer)
rt	room temperature; ca. 22-24 ˚C
sat.	saturated; as in a saturated aqueous solution
s	second(s)
TADDOL	(2*R*,3*R*)-2,3-O-(1-phenylethylidene)-1,1,4,4-tetra phenyl-1, 2,3,4-butanetetrol
TBAF	tetrabutylammonium fluoride
TBDMS or TBS	*tert*-butyldimethylsilyl
TBDMSCl or TBSCl	*tert*-butyldimethylsilyl chloride
TBDMSCN	*tert*-butyldimethylsilyl cyanide

TBS or TBDMS	*tert*-butyldimethylsilyl
t-BuLi	*tert*-butyllithium
TEA	triethylamine
TES	triethylsilyl
TESCN	triethylsilyl cyanide
TESOTf	triethylsilyl triflate
Tf	trifluromethanesulphonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran (oxolane)
TIPS	triisopropylsilyl
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TLC	thin-layer chromatography
TMS	trimethylsilyl or tetramethylsilane
TMSCl	trimethylsilyl chloride (chlorotrimethylsilane)
TMSCN	trimethylsilyl cyanide (cyanotrimethylsilane)
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Tol	toluene
Tr	triphenylmethyl (trityl)
TS	transition state
TsCl	4-methylbenzenesulfonyl chloride (toluenesulphonyl chloride)
v/v	volume relative to volume measured
w/v	weight relative to volume measured

1. Introduction

The cyathins are a unique group of diterpenoids produced by the bird's nest fungi *Cyathus helenae*, *C. africanus, and C. earlei*. Ayer and co-workers isolated the first natural product of this class in 1971 and several additional members of the family were discovered throughout the 1970's.[1-8] Several of the cyathins, especially cyathin B_3 and cyathin C_3, show strong antibiotic activity.[1,7]

More recently, several fungal metabolites with structures closely related to those of the cyathins have been reported. Kawagishi[9-11] isolated the analogous erinacines from *Hericium erinaceum*. The scabronines[12-14] and sarcodonins[15] have been isolated from *Sarcodon scabrosus*. Many of these recently discovered compounds have been shown to be potent stimulators of nerve growth factor (NGF) *in vitro*.[9-14]

1.1 Isolation and structure of the cyathanes

All of the cyathin diterpenoids were determined to possess a twenty-carbon skeleton containing a 5-6-7 fused tricyclic core, with the numbering scheme shown in **Figure 1**.

The isolated C_{20} compounds with 30 hydrogen atoms are classified as cyathin A derivatives. Those with 28 hydrogens are cyathin B derivatives and those with 26 hydrogens are members of the cyathin C class. The number of oxygen atoms is given by the subscript; thus, cyathin A_3 (**1**) is $C_{20}H_{30}O_3$. The prefixes *allo-* and *neoallo-* denote structural isomers of the

cyathin initially isolated.

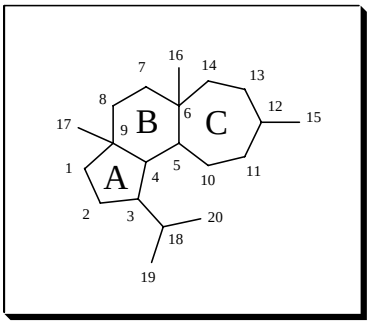
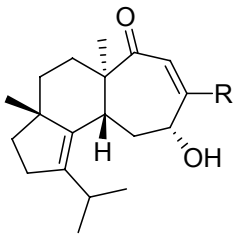


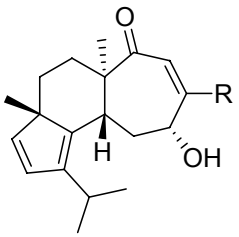
Figure 1. Cyathane numbering system

1.1.1 Isolation and structure of the cyathins

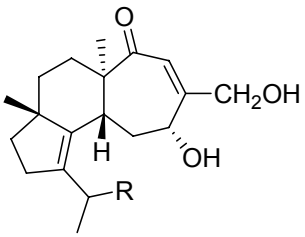
Cyathins were extracted from the culture broth of *Cyathus helenae*, a new species first discovered in the Canadian Rockies. [1]



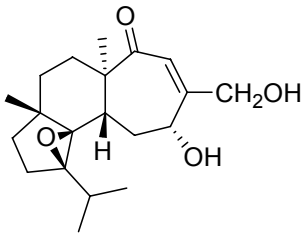
1 cyathin A_3 (R=CH_2OH)
2 cyathin B_3 (R=CHO)



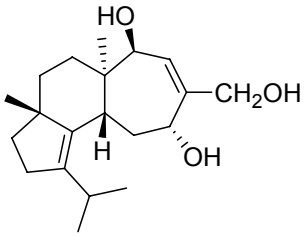
3 allocyathin B_3 (R=CH_2OH)
4 cyathin C_3 (R=CHO)



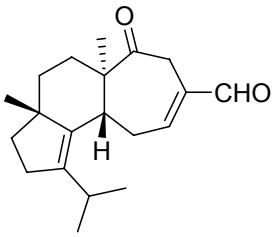
5 cyathin A_4 (R=CH_2OH)
6 cyathin C_5 (R=CO_2H)



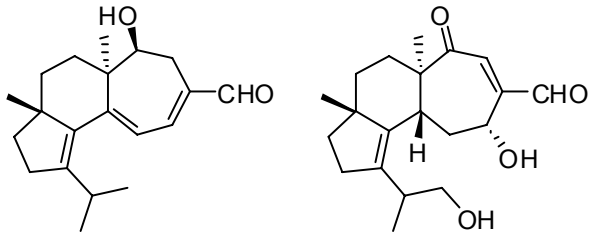
7 neoallocyathin A_4



8 cyathatriol



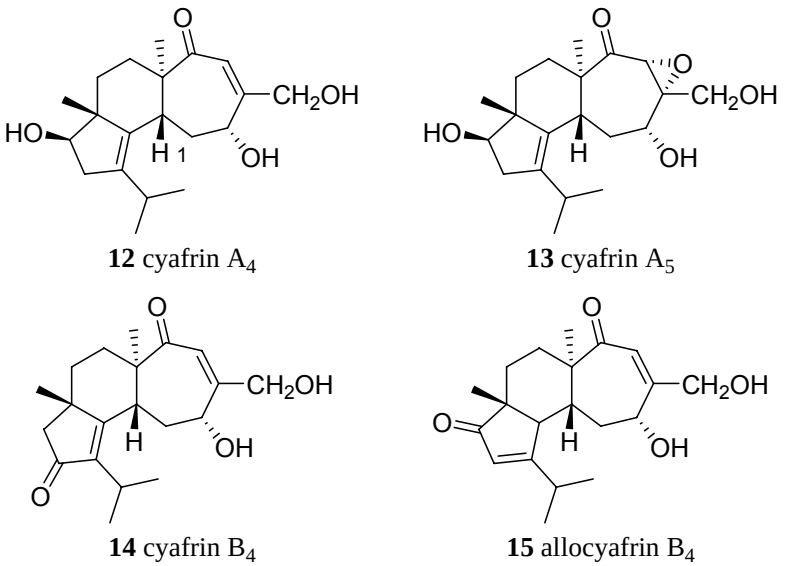
9 cyathin B_2



10 allocyathin B_2 **11**cyathin B_4

Figure 2. Structures of the cyathin diterpenes

Nine novel diterpenoids[2-8] (cyathin A_3, cyathin A_4 and allocyathin A_4, neoallocyathin A_4, cyathin B_3, cyathin B_4, cyathin C_5, allocyathin B_3, and cyathin C_3) were isolated and characterized. Cyathin A_3 is the major metabolite produced among these nine diterpenoids. The stereochemistry and absolute configuration of cyathin A_3 and allocyathin B_3 were established by X-ray crystallography and the structures of other cyathins (e.g **10** and **11**) were confirmed by chemical correlation with these known compounds or known derivatives thereof (**Figure 2**).



12 cyafrin A_4 **13** cyafrin A_5

14 cyafrin B_4 **15** allocyafrin B_4

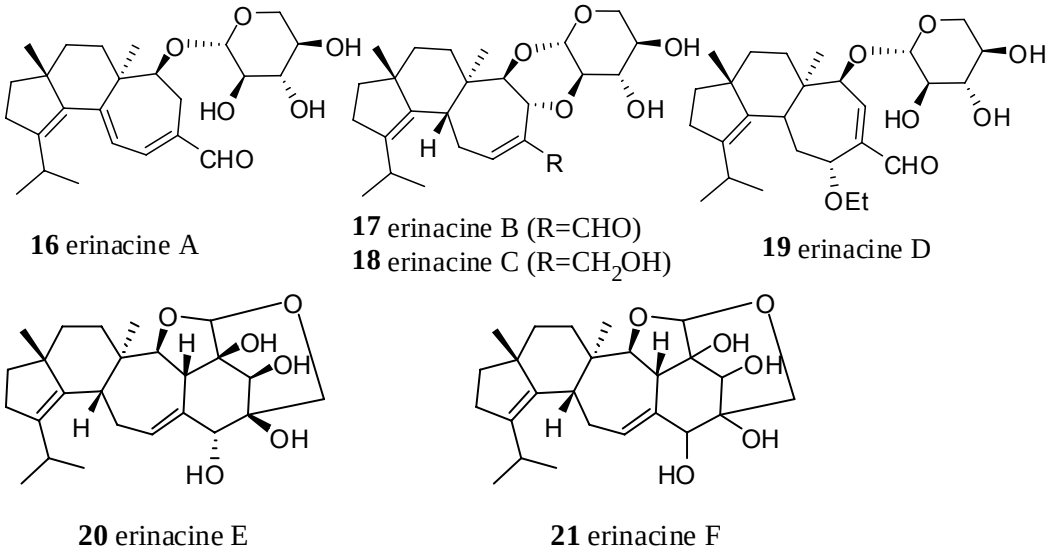
Figure 3. Structures of the cyafrin diterpenes

Cyathus africanus, a new species of the genus *Cyathus* from the area of Mount Kilimanjaro, Tanzania, was discovered by D. Hocking.[16] The ethyl acetate extract of the cultured broth of *C. africanus* provided six cyathin diterpenoids (cyathin A_3, allocyathin B_3, cyafrin A_4, cyafrin B_4, allocyafrin B_4, and cyafrin A_5) (**Figure 3**).

The structure of cyafrin A_4 (**12**) was confirmed by dehydration of the C-1 hydroxy group to give allocyathin B_3 (**3**), and the structure of cyafrin A_5 (**13**) was confirmed through epoxidation of cyafrin A_4 (**12**). Allocyafrin B_4 (**15**) was prepared from cyafrin A_4 (**12**) via oxidation followed by rearrangement of the double bond into conjugation in methanolic HCl.

1.1.2 Isolation and structure of the erinacines and striatins

Erinacines[9-11,17] were isolated from *Hericium erinaceum* and striatins were isolated from the mycelium of the basidiomycete *C. striatus* strain No.12. Erinacines and striatins[16] are glycosylated cyathins. These compounds are essentially comprised of a D-xylose moiety anchored onto the cyathin framework (**Figure 4**).



16 erinacine A

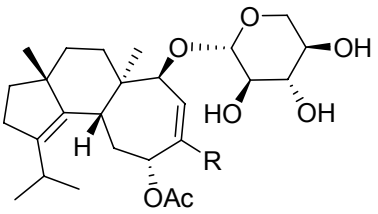
17 erinacine B (R=CHO)
18 erinacine C (R=CH_2OH)

19 erinacine D

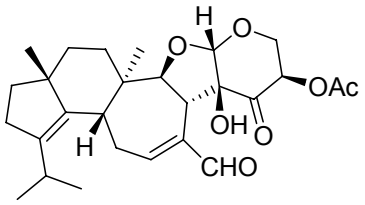
20 erinacine E

21 erinacine F

Figure 4. Structures of erinacines A-F



22 erinacine P (R=CHO)
23 erinacine Q (R=CH_2OH)

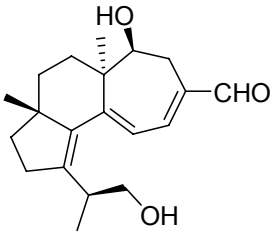


24 striatal A

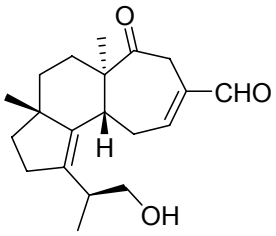
Figure 5. Structures of erinacines P and Q and striatal A

1.1.3 Isolation and structure of the sarcodonins and scabronines

Sarcodonins[18,19] and scabronines [12-14] are two families of diterpenes closely related to cyathins, that were isolated from the mushroom *Sarcodon scarbrosus*. The major difference between these compounds and the cyathins is the oxidation state of C20 in the sarcodonins (**Figure 5**) and C17 in the scabronines (**Figure 6**).



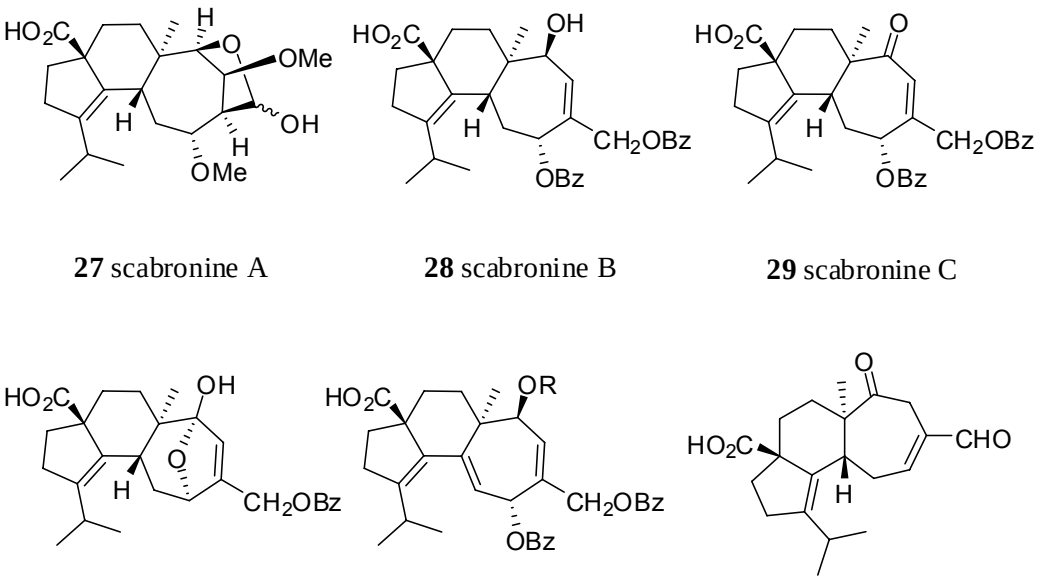
25 sarcodonin A



26 sarcodonin G

Figure 6. Structures of the sarcodonins

Although there have been eight sarcodonins discovered (sarcodonins A-H), only the structures of sarcodonin A and G have been established. [15]



27 scabronine A **28** scabronine B **29** scabronine C

30 scabronine D **31** scabronine E (R=Ac) **32** scabronine F (R=H) **33** scabronine G

Figure 7. Structures of the scabronines.

1.2 Biological activities of the cyathanes

Allocyathin B_3 and cyathin C_3 exhibited antibiotic activity against Gram positive and Gram negative bacteria as well as actinomycetes. A renewed interest in this class of natural products was initiated by the discovery that members of the erinacine and scabronines class stimulate the biosynthesis of nerve growth factor (NGF).[9-13,17,20-24]

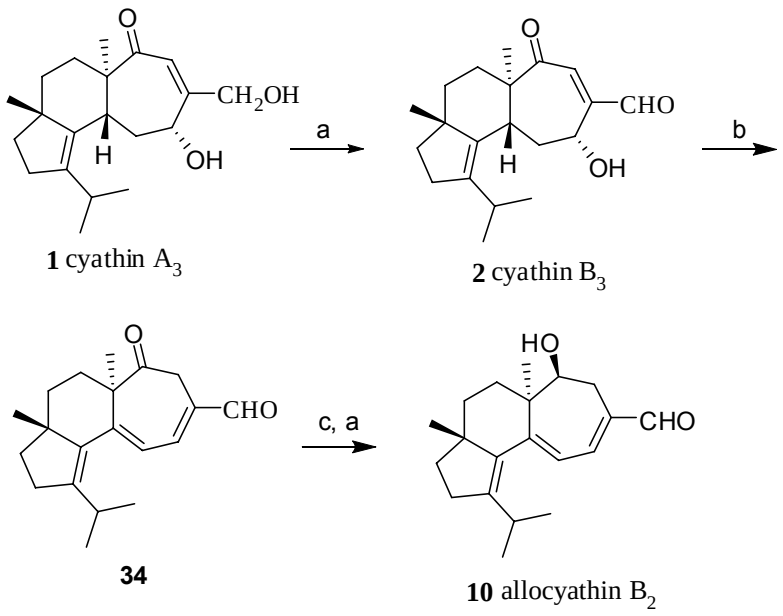
In a bioassay using mouse astroglial cells in the presence of erinacines A, B, and C, the amounts of NGF detected in the culture medium were four fold, two fold, and five fold higher than in the presence of epinephrine, a known potent NGF stimulator used as a positive control-compound in the assay. Moreover, erinacine E was recently shown to not only have potent NGF synthesis-stimulating activity, but also κ-opioid receptor agonist activity.[11]

1.3 Synthetic transformations of the cyathanes

1.3.1 Transformation of cyathin A_3 into cyathin B_3, allocyathin B_2 and neoallocyathin A_4

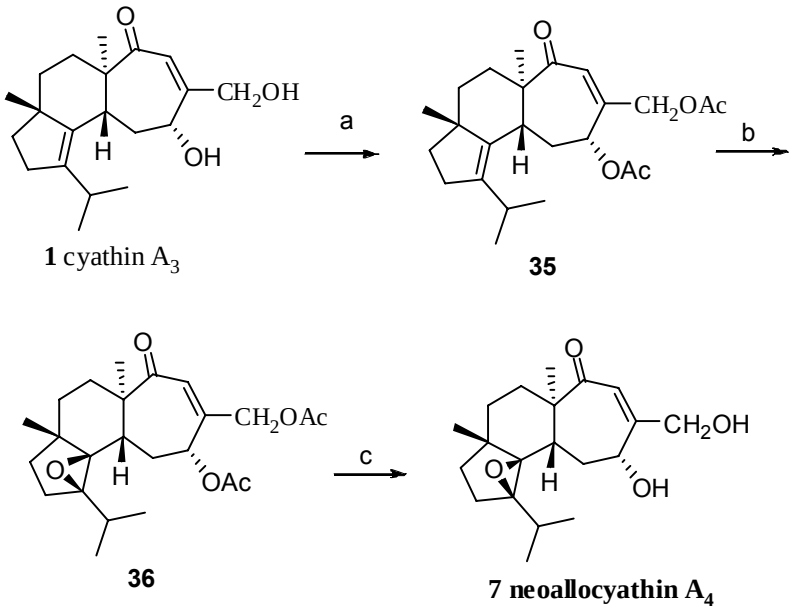
Cyathin A_3 was the most abundant metabolite isolated from *Cyathus helenae* and from *Cyathus africanus*. The transformation of cyathin A_3 into other cyathins was, therefore, of interest.

Scheme 1



(a) MnO_2; (b) Ac_2O, Py; (c) $LiAlH_4$.

Scheme 2



1 cyathin A_3 **35** **36** **7 neoallocyathin A_4**

(a) Ac_2O, Py; (b) *m*-CPBA; (c) K_2CO_3

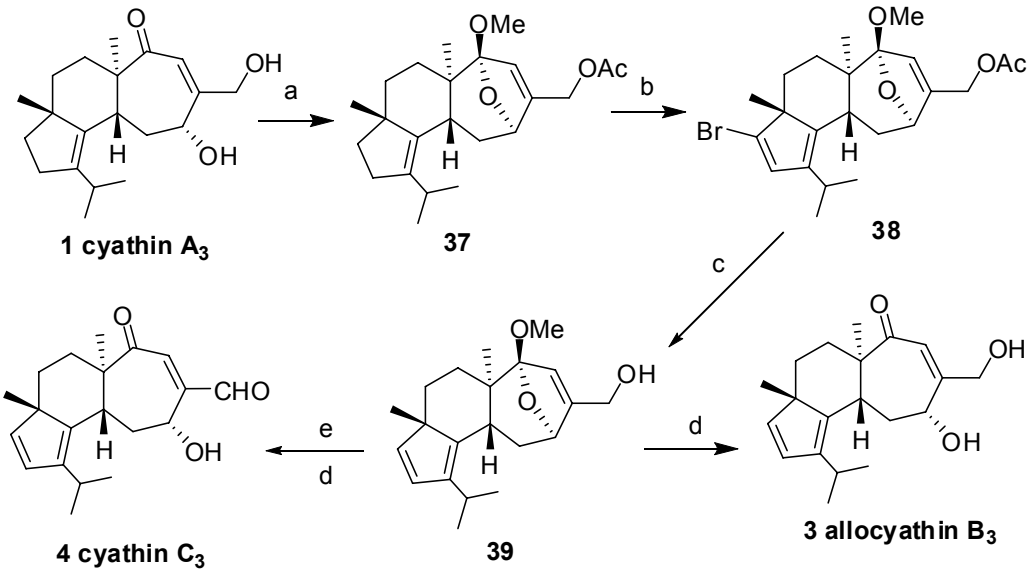
Selective oxidation of cyathin A_3 with manganese dioxide in ether provided cyathin B_3. Treatment of cyathin B_3 with pyridine and acetic anhydride gave both cyathin B_3 acetate and triene **34**. Allocyathin B_2 was easily prepared by reducing triene **34** with $LiAlH_4$. Epoxidation of cyathine A_3 acetate followed by deprotection yielded neoallocyathin A_4.[7]

1.3.2 Transformation of cyathin A_3 into allocyathin B_3 and cyathin C_3

The key step in the transformation of cyathin A_3 into allocyathin B_3 involved the formation of bromodiene **38** by treatment of the protected cyathin A_3 derivative **37** with NBS in the presence of benzoyl peroxide. Sequential dehalogenation and deprotection furnished allocyathin B_3 (**3**). Alternatively, cyathin C_3 (**4**) could be similarly obtained by careful oxidation of the

hydroxyl group in **39** and hydrolysis (**Scheme 3**).

Scheme 3

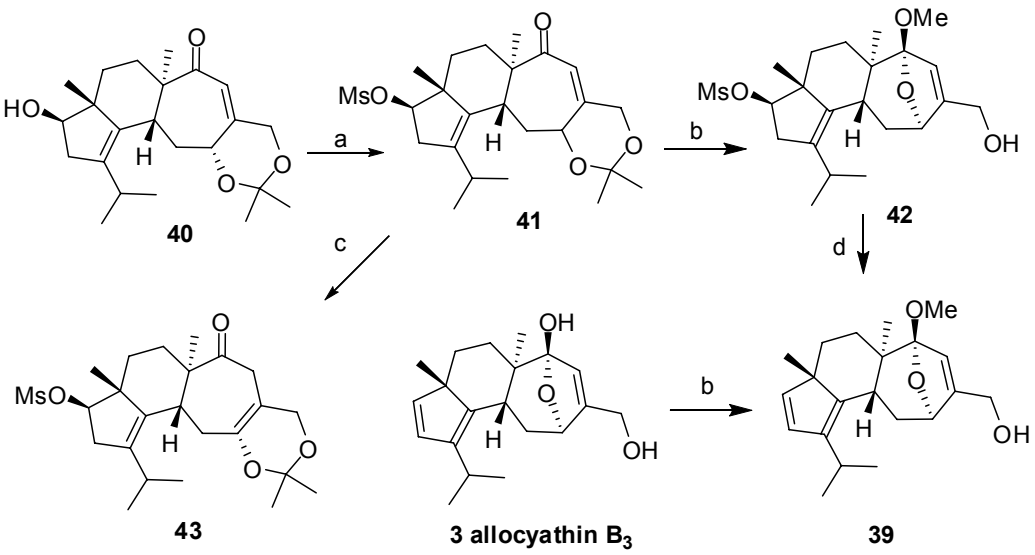


(a) i, MeOH, HCl; ii, Ac_2O, Py; (b) 2eq NBS, CCl_4, $(Bz)_2O_2$ Δ; (c) $LiAlH(OCH_3)_3$, CuI, THF; (d) H_3O+; (e) MnO_2, Et_2O;

1.3.3 Transformation of cyafrin A_4 into allocyathin B_3 methyl ketal and allocyafrin B_4 methyl ketal

In order to correlate cyafrin A_4 (**12**) with allocyathin B_3 (**3**), the C-1 hydroxy group was mesylated after protection the two hydroxyl groups on the C-ring as an acetonide (**Scheme 4**). Treatment of the resulting mesylate **41** with DBU did not promote elimination but led to the deconjugated ketone **43**. After transformation of **41** into methyl acetal **42**, prolonged refluxing with DBU provided the desired A-ring diene **39**, which was identical to the one prepared alternatively from allocyathin B_3 (**3**) by treatment with methanolic HCl.

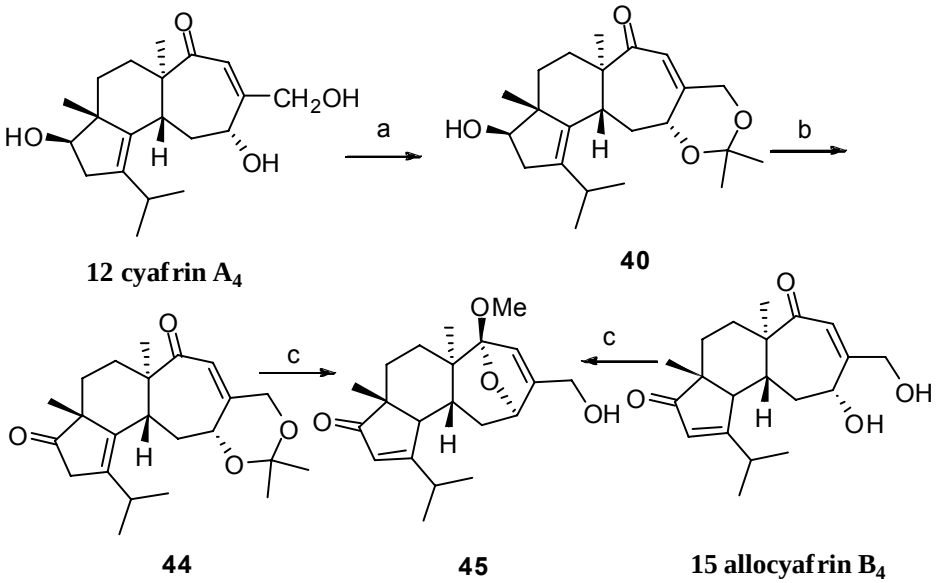
Scheme 4



(a) MsCl, Py; (b) CH_3OH, HCl; (c) DBU, dioxane, Δ; (d) DBU, toluene, Δ 45h.

Alternatively, acetonide **40** was oxidized to ketone **44**, which gave allocyafrin B_4 methyl acetal **45** after isomerization of the double bond to the C-2,3 position (**Scheme 5**).

Scheme 5



(a) $(CH_3)_2C(OCH_3)_2$, p-TsOH, r.t.; (b) Jones' oxidation; (c) CH_3OH, HCl.

1.4 Synthetic studies on cyathanes

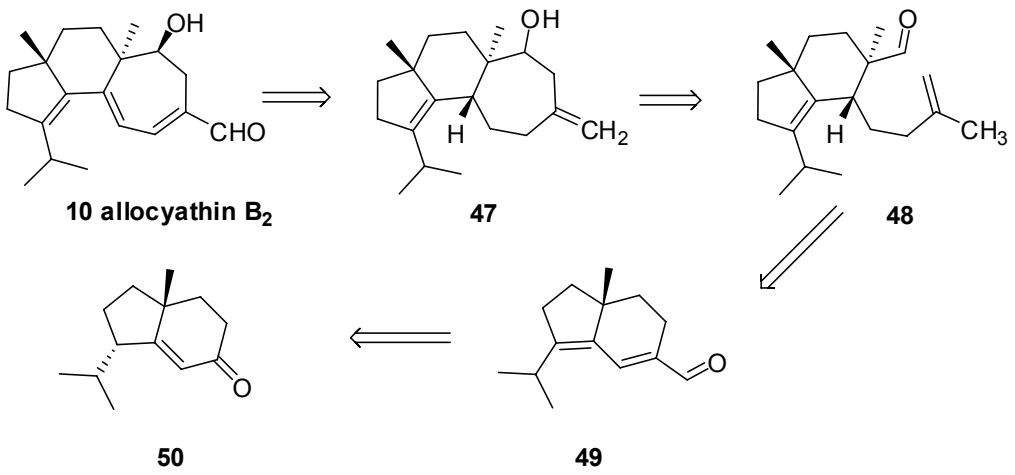
From a synthetic point of view, the key structural features of cyathanes include: the 5-6-7 tricyclic ring system, the *anti*-1,4 methyl groups at quaternary carbons C6 and C9, the extensive oxygenation on ring–C, and the *trans* 6-7 ring fusion.

To date, there have been seven total syntheses and six partial syntheses of cyathins. Most of these syntheses target allocyathin B_2 (**10**), which does not contain the common 6-7 *trans* ring fusion, or the hydroxyl group at carbon 11. Modifications of these routes to provide targets with these features have not been demonstrated and may be challenging.

1.4.1 Snider's synthesis

Snider[25,26] was able to achieve the first total synthesis of racemic allocyathin B_2 and (+)-erinacine A (**16**) (**Scheme 6**).

Scheme 6



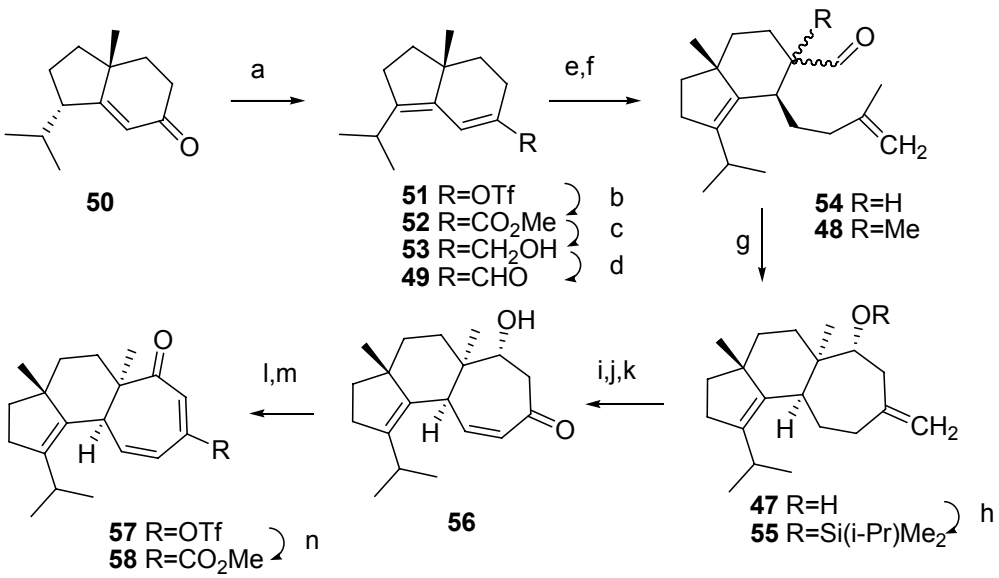
10 allocyathin B_2 **47** **48**

50 **49**

Snider adopted a linear synthetic sequence that involved consecutive

assembly of the A, B and C rings. The key step involved a Me_2AlCl initiated intramolecular carbonyl-ene cyclization.[27] Snider envisioned that the alcohol **47** was an advanced intermediate for the synthesis of allocyathin B_2, which could be obtained from aldehyde **48**. The ene substrate was designed from enal **49**, which would be derived from readily available **50**.[28]

Scheme 7

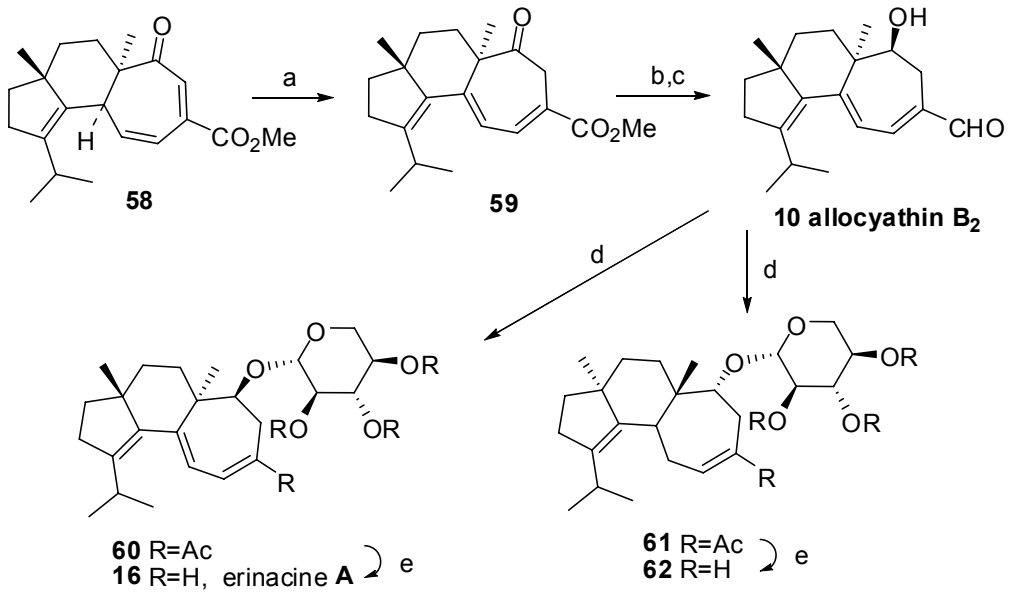


(a) Proton Sponge, Tf_2O, 88%; (b) $Pd(OAc)_2$, Ph_3P, CO, i-Pr_2EtN, 85%; (c) DIBAL, 97%; (d) MnO_2, 95%; (e) $H_2CC(CH_3)(CH_2)_2MgBr$, CuBrDMS, TMSCl, 91%; (f) ^tBuOK, MeI, 75%; (g) Me_2AlCl, 87%; (h) i-$Pr(Me)_2SiCl$, imid., 95%; (i) OsO_4, KIO_4, 77%; (j) LHMDS, PhSeCl, H_2O_2, 72%; (k) AcOH, H_2O; (l) Dess-Martin, 72% 4 steps; (m) KHMDS, $PhNTf_2$, 75%; (n) $Pd(OAc)_2$, Ph_3P, CO, $^iPr_2EtN$, 75%.

The synthetic approach commenced with palladium-catalyzed carbonylation of the enol triflate **51** (**Scheme 7**), which was readily prepared from the previously reported enone **50** (available in 2 steps). The resulting dienoate **52** was reduced and reoxidized to give aldehyde **49**. Copper(I)-catalyzed conjugate addition of pentenyl magnesium bromide to

49 gave **54** as a mixture of epimers at C6.[29] The stereoselectivity of the cuprate addition was unfortunate because the incorrect stereochemistry was generated at C5.[30-32] However, subsequent methylation of **54** provided the desired product **48** as a prelude to C-ring closure. The intramolecular carbonyl ene reaction proceeded readily to form the C13-C14 bond and give the alcohol **47** containing the complete cyathane skeleton but with a *cis* B-C ring fusion. Oxidative cleavage of the exocyclic methylene in **47** was followed by conversion to the enone **56** by a selenation-elimination sequence after alcohol deprotection. Alcohol **56** was oxidized and the resulting β-diketone was converted selectively to the enol triflate **57** upon treatment with N-phenyltriflimide. Installation of the remaining carbon of the cyathin system was accomplished via palladium-catalyzed carbonylation to provide the methyl ester **58** in good yield.

Scheme 8



(a) Et_3N, MeOH, 94%; (b) LAH, 89%; (c) MnO_2, 94%; (d) triacetyl-a-D-xylopyranosyl bromide, $Hg(CN)_2$, $HgCl_2$, 34%; (e) K_2CO_3, MeOH, >90%.

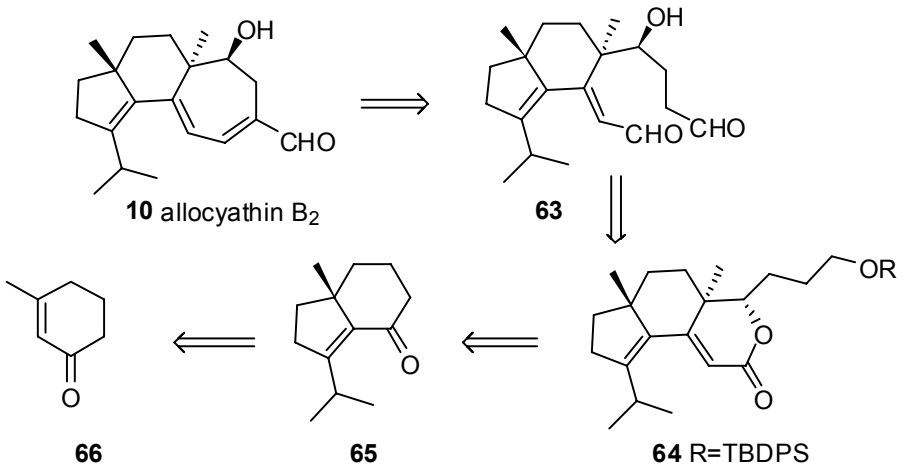
With key intermediate **58** in hand, the stage was set for the final

manipulation of the peripheral functionality to complete the total synthesis (**Scheme 8**). Isomerization of **58** under basic conditions gave the non-conjugated ketone **59** and removed the undesired stereochemical arrangement at C5. Global reduction of **59** was followed by selective oxidation of the allylic alcohol to give racemic allocyathin B_2 (**10**). Glycosylation of racemic **10** with α-bromo-2,3,4-tri-O-acetyl-D-xylopyranose provided erinacine A triacetate (**60**) and the diastereomer **61**. The two diastereomers were separated and deprotected to give erinacine A (**16)** and **62,** respectively. This synthetic approach delivered **10** and **16** in 17 and 19 steps, respectively.

1.4.2 Tori's synthesis

The general features of Tori's[33] synthesis of racemic allocyathin B_2 are summarized in Scheme 9. Tori's synthetic strategy involved the construction of both the A ring and the C ring via two aldol cyclizations. The assembly of the highly functionalized seven-member ring was deferred to the last stage in the synthesis.

Scheme 9

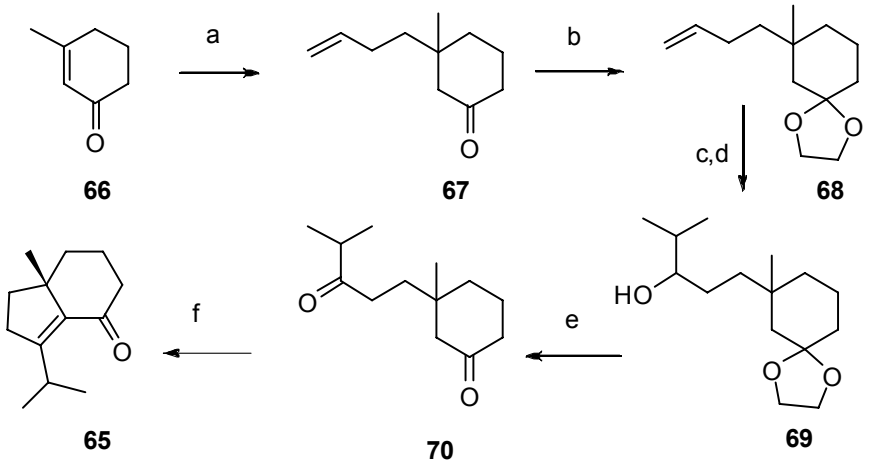


10 allocyathin B_2 **63** **64** R=TBDPS **65** **66**

The synthetic objective became **63** and it was anticipated that this substance could be derived from intermediate **64** through a straightforward sequence of reactions. Removal of the side chain appendages from lactone **64**, the projected precursor of dialdehyde **63**, reveals hydrindenone **65**, which could be derived from 3-methylcyclohexenone.

Tori began the synthesis by conversion of readily available 3-methylcyclohexenone (**66**) in 5 steps to diketone **70** (**Scheme 10**). Treatment of diketone **70** with base followed by dehydration generated the desired hydrindenone **65**.

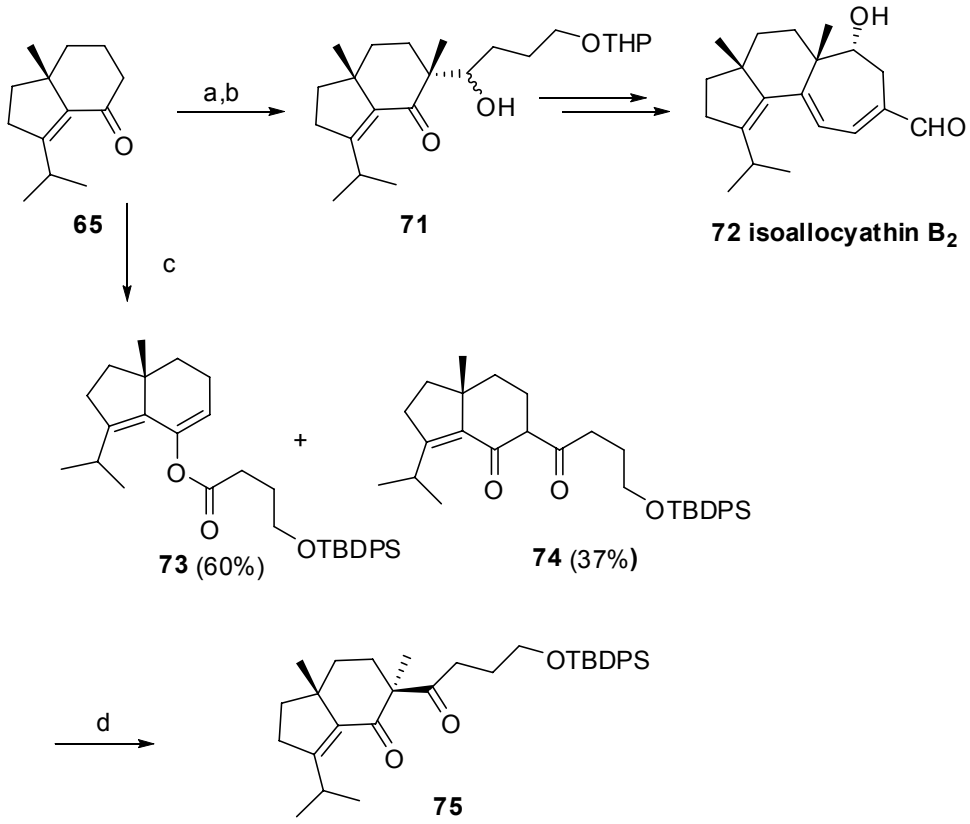
Scheme 10



(a) $CH_2CHCH_2CH_2MgBr$, CuBrDMS, THF; (b) $HOCH_2CH_2OH$, TsOH, PhH, 88% 2 steps; (c) O_3, Zn, AcOH; (d) i-PrMgBr, 83%; (e) Jones oxidation; (f) 5%-KOH, MeOH, 73% 2 steps.

The stage was then set for stereoselective addition of the methyl group and the side chain. The initial assumption was that alkylation of **65** at the C-11 position would occur from the convex face of the ring, which turned out to be wrong. Methylation of **65** followed by aldol condensation with the four carbon aldehyde[34] gave the wrong stereoisomer and eventually led to isoallocyathin B_2 (**72**) (**Scheme 11**).[35] After considerable experimentation, it was discovered that the desired diketone **75** could be prepared by methylation of diketone **74**, the product of C-acylation of ketone **65**.

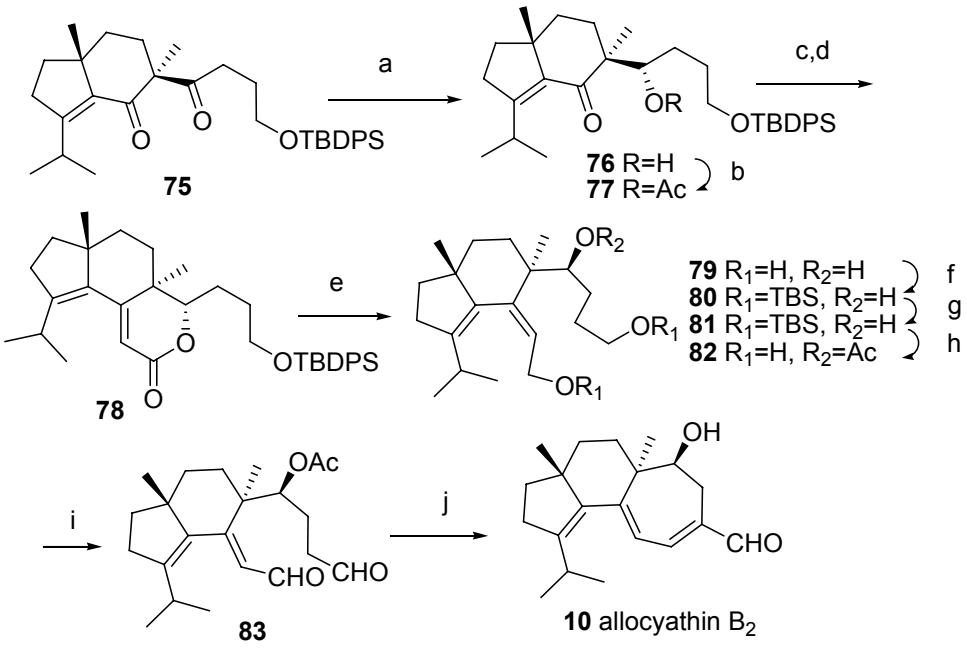
Scheme 11



(a) LDA, MeI, THF; (b) LDA, THF, $HCO(CH_2)_3OTHP$, 20%; (c) LDA, THF $ClCO(CH_2)_3OTBDPS$, -78°C, 37%; (d) ^tBuOK, MeI, 91%.

Diketone **75** was regioselectively and stereoselectively reduced with zinc borohydride to afford **76**,[36] which was converted to the corresponding acetate **77** (**Scheme 12**). Intramolecular aldol reaction of **77,** followed by dehydration with thionyl chloride provided the unsaturated lactone **78**. The lactone **78** was reduced with $LiAlH_4$ to give the triol **79**. After protecting group manipulations, diol **82** was oxidized to the corresponding dialdehyde **83** via Swern oxidation. Intramolecular aldol cyclization of **83** completed the total synthesis of racemic allocyathin B_2 in 18 steps.

Scheme 12

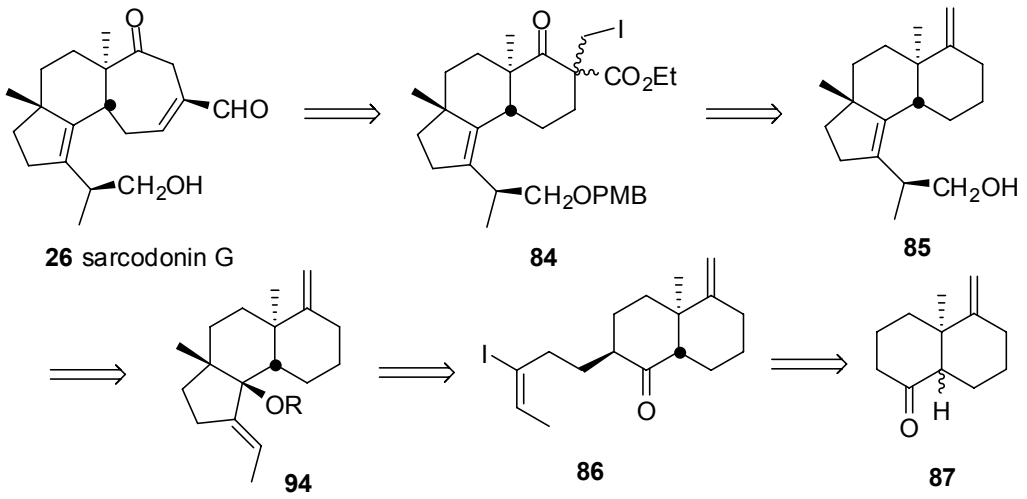


(a) $Zn(BH)_4$, Et_2O, -78°C; (b) Ac_2O, DMAP, pyridine; (c) LHMDS, THF, -78°C; (d) $SOCl_2$, pyridine, DCM; (e) LAH; (f) TBSCl, Et_3N, 37% 2 steps; (g) Ac_2O, DMAP, Py; (h) PPTS, MeOH, 52%, 2 steps; (i) Swern; (j) 5%-KOH MeOH, 74%, 2 steps.

1.4.3 Piers' synthesis

Piers'[37] synthetic target was sarcodonin G, a highly functionalized member of the cyathane family of diterpenoids, that contains a *trans*-fused B-C ring system. The general features of Piers' synthesis are outlined retrosynthetically in **Scheme 13**. The key steps involved the stereoselective cyclization of iodoketone **86,** Still-Mitra [2,3]-sigmatropic rearrangement[38] to generate allylic alcohol **85**, and the SmI_2-induced ring expansion of α-iodomethylketone **84** to provide the cyathane carbon skeleton.

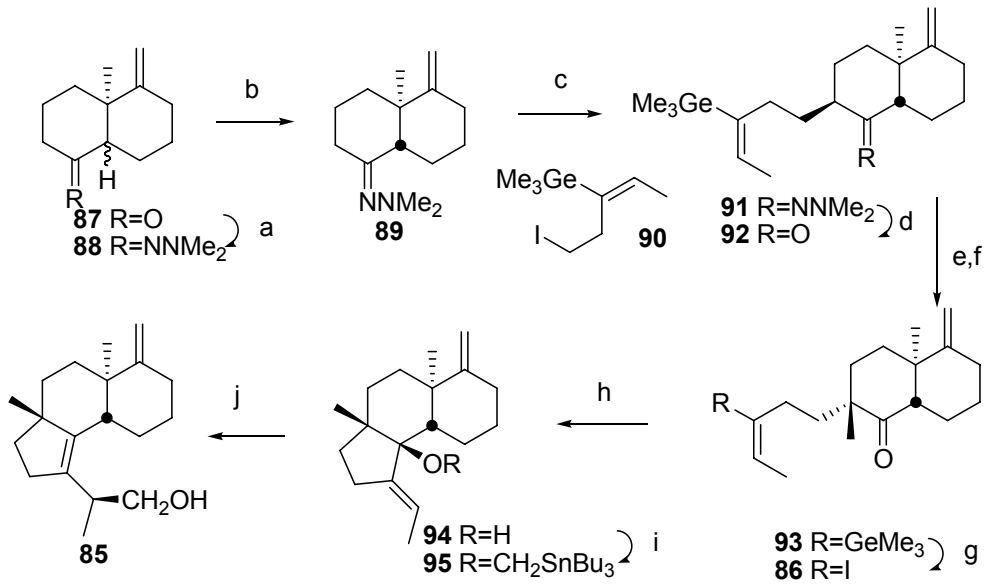
Scheme 13



Piers' synthesis started with the known mixture (*trans*:*cis* ~3.5:1) of decalones **87**, that were converted to the corresponding mixture of dimethylhydrazones **88** (*trans*:*cis* ~1:1) (**Scheme 14**). CSA-catalyzed equilibration of **88** followed by chromatography provided the *trans*-fused dimethylhydrazone **89**. Alkylation of the anion of **89** with iodide **90** gave hydrazone **91**.[39,40] The iodide **90** was prepared from ethyl pent-2-ynoate via germylation,[41] deconjugation,[42] reduction, and iodination in six steps. After hydrolysis of the hydrazone **89**, the resulting ketone **92** was first treated with sodium methoxide to isomerize the side chain to the equatorial position and then a methyl group was stereoselectively added by alkylation of the corresponding enolate to obtain **93**. Thus, the *anti* relationship between methyl groups at C9 and C6 was established.

Subjecting alkenyltrimethylgermane **93** to NIS provided the iodo-alkene **86**.[43] Metal-halogen exchange on **86** triggered an intramolecular addition to the carbonyl, which furnished the tricyclic alcohol **94**.[44] Sequential treatment of the tertiary allylic alcohol **94** with KH and tributylstannylmethyl iodide generated α-stannyl ether **95**. Lithiation of **95** followed by Still-Mitra [2,3]-sigmatropic rearrangement to **85** stereoselectively introduced the hydroxmethyl group and established the C3-C4 olefin in one operation.[38,45]

Scheme 14

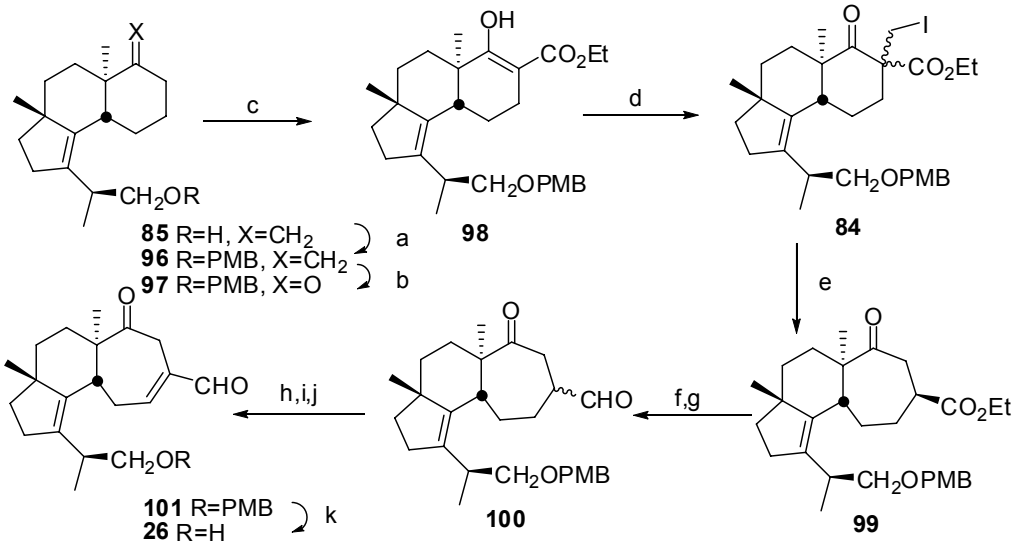


(a) Me_2NNH_2, CSA, 82%; (b) CSA, PhH, reflux; (c) KDA, DMPU, **90**; (d) HOAc, NaOAc, 69% 3 steps; (e) NaOMe, MeOH, 82%; (f) $LiNEt_2$, CH_3I, 85%; (g) NIS, CH_2Cl_2, 90%; (h) BuLi, 86%; (i) KH, 18-Crown-6, Bu_3SnCH_2I; (j) BuLi, 88% 2 steps.

With key intermediate **85** in hand, the stage was set for the final expansion of ring C and installation of the required peripheral functionality (**Scheme 15**). Protection of the primary alcohol in **85** as a PMB ether and chemoselective oxidative cleavage of the exocyclic double bond provided ketone **97**. Ethoxycarbonylation of **97** followed by alkylation with diiodomethane gave a diastereomeric mixture of iodomethyl keto-esters **84**. Subjecting **84** to samarium(II) iodide initiated a one carbon ring expansion[35] providing cycloheptanone **99**. Sequential reduction and oxidation of **99** gave keto-aldehyde **100**. Treatment of **100** with piperidine, followed by PhSeCl, gave a diasteromeric mixture of selenides that, on oxidation, produced a regioisomeric mixture of alkenes that isomerized to enal **101** under basic conditions. Removal of the PMB group in **101** with DDQ

completed the total synthesis of racemic sarcodonin G (**26**) in 21 steps from decalin **87**.

Scheme 15

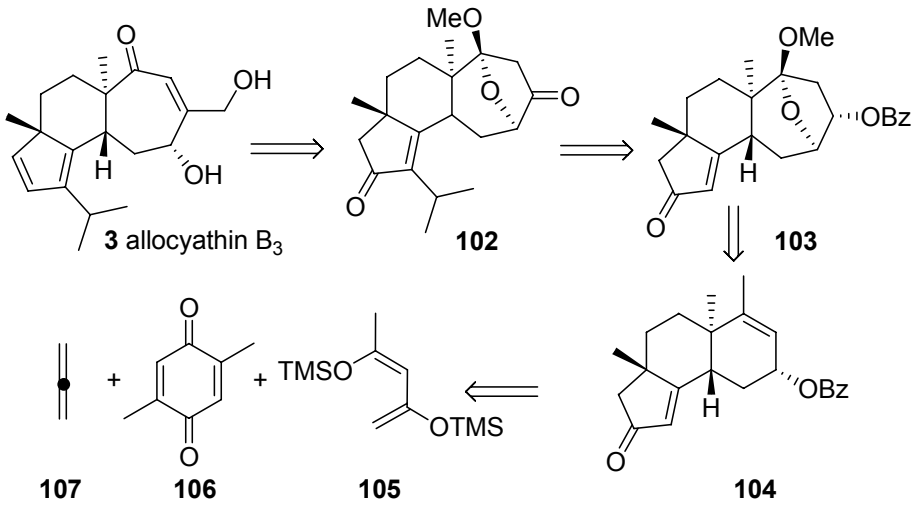


(a) KH, PMBCl, TBAI, 96%; (b) OsO_4, KIO_4, 85%; (c) KH, NaH, $(EtO)_2CO$, 74%; (d) TBAF, CH_2I_2, 78%; (e) SmI_2, 71%; (f) DIBAL-H; (g) Dess-Martin, 86% for 2 steps; (h) piperidine, PhH then PhSeCl; (i) KIO_4, 78% for 2 steps; (j) DBN, PhH, 95%; (k) DDQ, H_2O, 91%.

1.4.4 Ward's synthesis

The first published synthetic approach to cyathins was developed by Ayer and Ward, which provided a key 5-6-6 tricyclic intermediate.[46] Ward extended this work and was able to accomplish the total synthesis of racemic allocyathin B_3.[47] Ward's synthesis was the first general route providing both the *trans* 6-7 ring fusion and the fully functionalized seven-membered ring, that with simple modifications might be applied to the synthesis of *any* of the known cyathin diterpenes, as well as several related natural products.

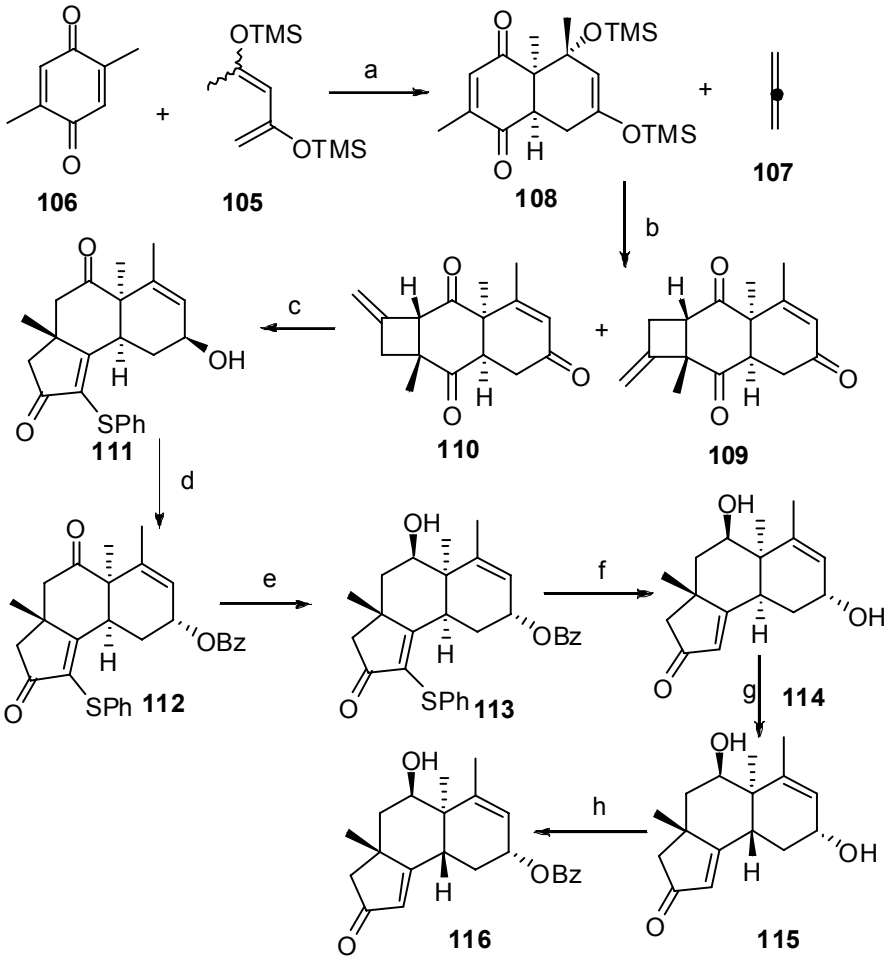
Scheme 16



The general features of Ward's synthesis are outlined retrosynthetically in Scheme 16. The key steps involved [2+2] cycloaddition followed by intramolecular aldol addition to form the A-ring; [4+2] cycloaddition followed by ring expansion to form the C-ring and intramolecular radical cyclization to introduce the isopropyl group.

Ward's synthesis commenced with the Diels-Alder reaction of 2,5-dimethylbenzoquinone **106**[48,49] with diene **105** (a 1:1 mixture of diastereomers)[50] to yield the adduct **108** as a single stereoisomer (**Scheme 17**). Photochemical [2+2] addition of **108** to allene provided a 4 : 1 mixture of regioisomeric methylene cyclobutanes **109** and **110** with the desired **110** as the major product. Thus installation of the *anti* methyl groups at C-6 and C-9 was accomplished in two steps. The relative stereochemistry was controlled by the face selectivity of the sequential cycloadditions.

Scheme 17

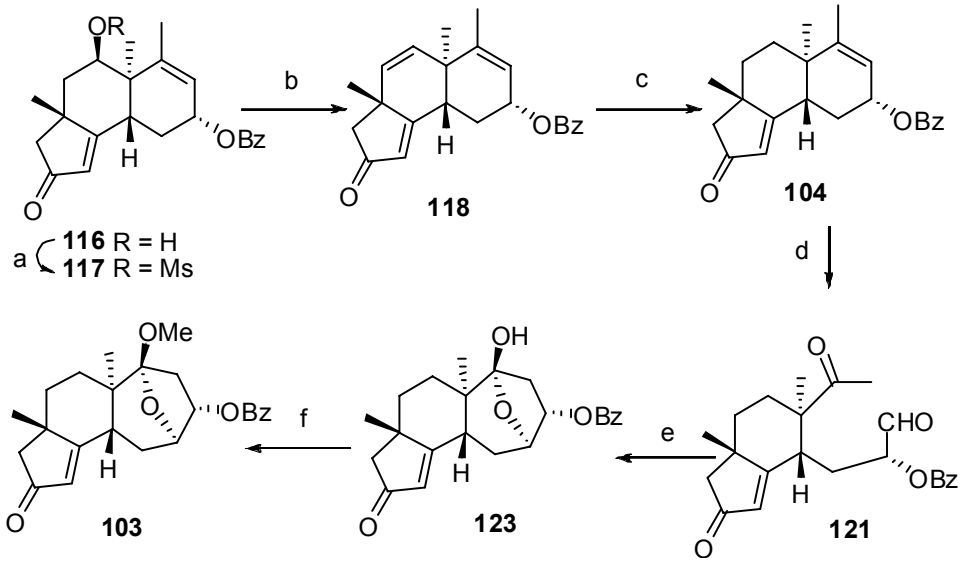


(a) 140°C (92%); (b) i. allene, hν; ii. TFA; (c) i. *m*-CPBA; ii. 9-BBN; iii. PhSH, NaOH (50% from **108**); (d) PhCOOH, DEAD, Ph_3P; (e) $NaBH_4$, CH_2Cl_2, MeOH, -78°C; (f) i. NaOH, MeOH; ii. RaNi; (g) NaOH, MeOH, reflux; (h) BzCl, Et_3N, DMAP (60% from **111**).

Epoxidation of the hydrolyzed photoadducts **109** and **110** followed by selective 1,2 reduction of the enone and fragmentation of the epoxide with thiophenol under basic conditions formed cyclopentenone **111** in one operation. The hydroxyl group at C11 was inverted under Mitsunobo conditions to yield **112**. Chemoselective reduction[51] of dione **112** gave **113**. After hydrolysis of the benzoate in **113**, desulfurization with Raney nickel

furnished the enone **114**. Treatment of **114** with sodium hydroxide successfully isomerized the *cis*-ring fusion to the *trans*-ring fusion to provide **115**. Chemoselective benzoylation of diol **115** gave key intermediate **116**.

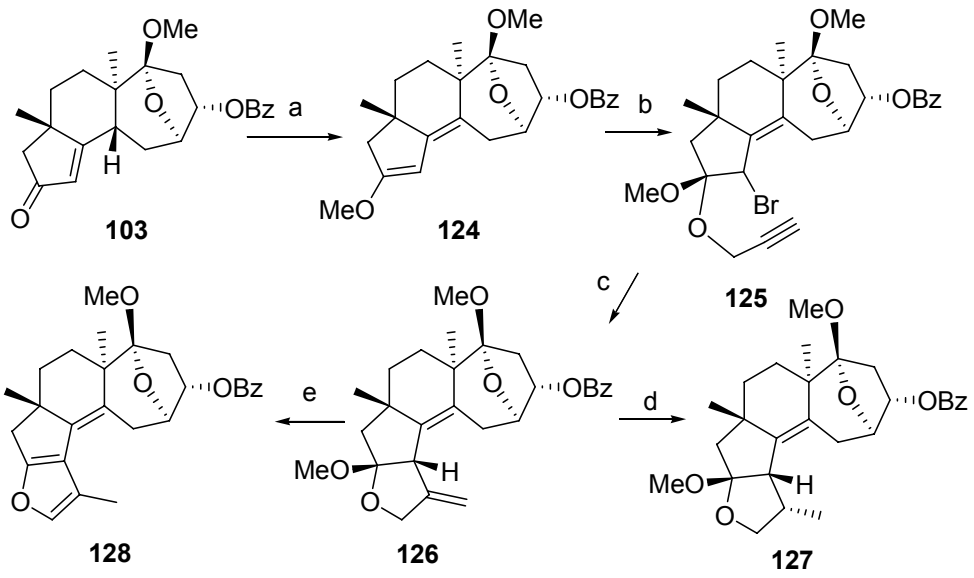
Scheme 18



(a) MsCl, pyridine, 50°C (93%); (b) DBU, toluene reflux (75%); (c) H_2, $RhCl(Ph_3P)_3$ (90%); (d) O_3, Sudan III, then Me_2S; (e) TsOH, toluene; (f) MeI, Ag_2O (50% from **104**).

Removal of the now unwanted hydroxyl group at C7 in **116** was achieved by mesylation followed by elimination of the mesylate and chemoselective reduction of the resulting olefin to provide **104** (**Scheme 18**). The next stage in the synthetic sequence involved expansion of six-membered ring to furnish the required seven-membered C-ring system. Selective ozonolysis of the non-conjugated double bond in **104** was achieved by ozonolysis in the presence of Sudan(III)[52] as an indicator. Treatment of the resulting keto-aldehyde **121** with acid triggered the sequential aldol condensation and benzoyl group migration. After methylation of the hemiacetal, the key intermediate **103** was obtained, containing the complete 5-6-7 cyathane ring system with correct relative stereochemical configuration at all positions.

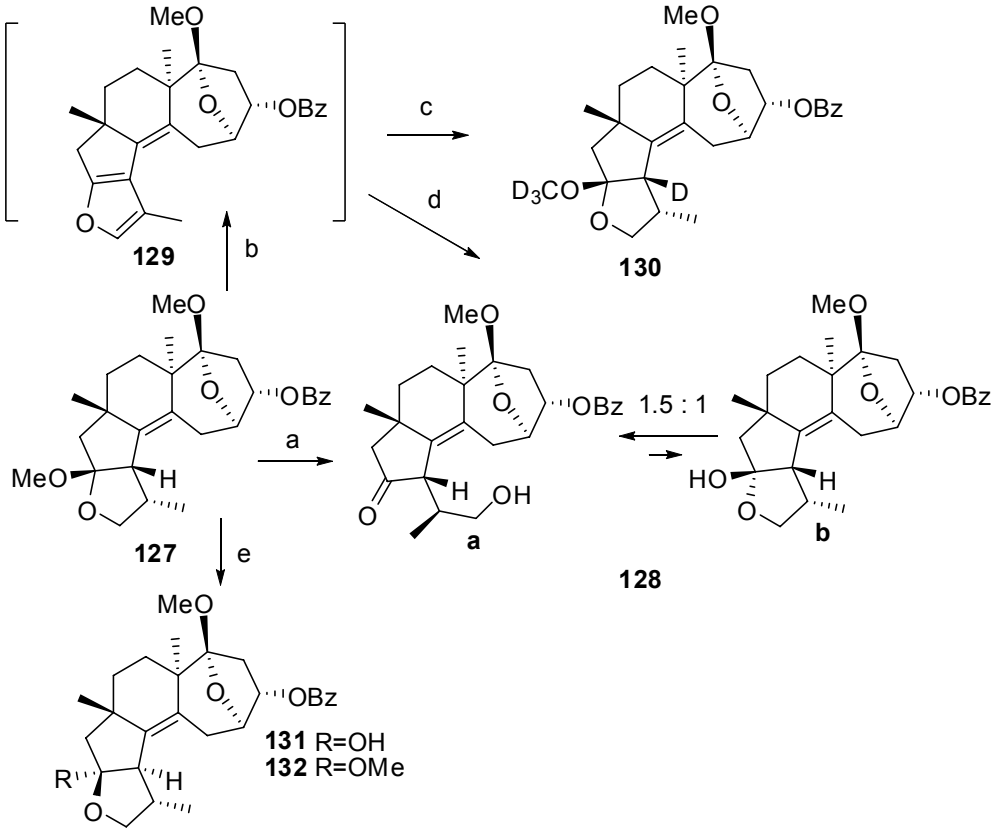
Scheme 19



(a) MeOH, HCl, $(MeO)_3CH$, toluene, reflux; (b) NBS, propargyl alcohol, CH_2Cl_2, -78°C; (c) Ph_3SnH, AIBN, C_6H_6, reflux (60% from **103**); (d) H_2, Pd-C, EtOAc (90%). (e) TMSCl, NaI.

Strategies to introduce the isopropyl group at C-3 of **103** were not obvious. After considerable experimentation, a method was established to introduce a 3-carbon side chain based on radical cyclization (**Scheme 19**). Treatment of **103** with trimethyl orthoformate and methanolic HCl in toluene followed by azeotropic distillation of MeOH produced dienol ether **124**. Cohalogenation[53] of **124** with NBS and propargyl alcohol gave the somewhat unstable **125** as a single diastereomer, which cyclized[54] to **126** on treatment with Ph_3SnH and AIBN in refluxing benzene. Unmasking the isopropyl group present in **126** proved to be difficult. Because of the facile formation of **128** from **126**, efforts were directed at unraveling the reduced derivative **127,** easily repared by hydrogenation of **126**.

Scheme 20



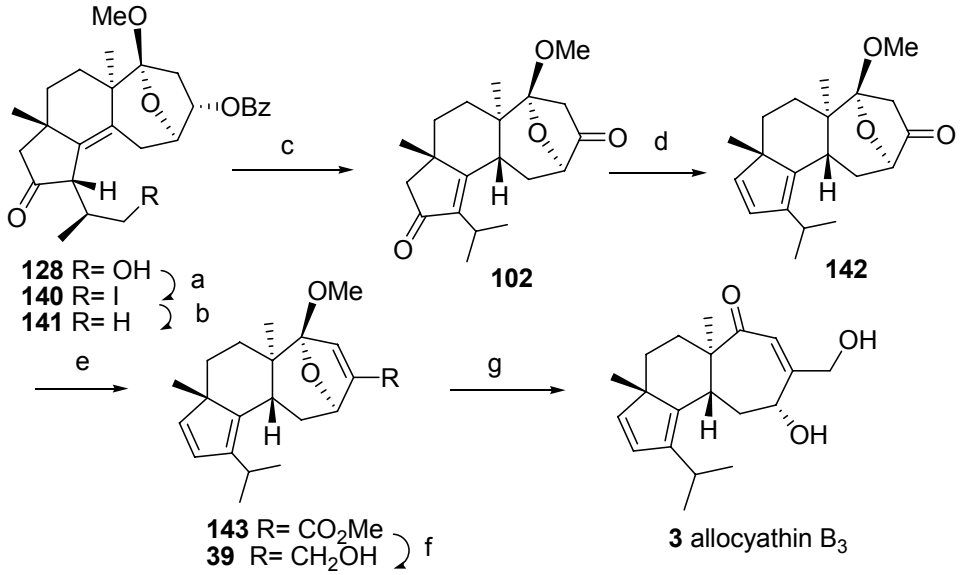
(a) PPTS, acetone, H_2O, rt, 12 day (75%; quantitative based on conversion).

Exposure of **127** to 10% aq. HCl in THF slowly (ca. 14 h) produced the isomerized hemiacetal **131** without evidence of an intermediate (**Scheme 20**) (by TLC monitoring). Unfortunately, all attempts to trap the hydroxy ketone tautomer of hemiacetal **131** failed.

A serendipitous observation was crucial to the successful synthesis (**Scheme 20**). On one occasion, hydrogenation of **126** under the usual conditions unexpectedly gave **128** (25%) along with **127**. In contrast to **131**, **128** was a 1.5:1 mixture (by NMR in $CDCl_3$ solution) of the hydroxy ketone (**128a**) and hemiacetal (**128b**) tautomers, respectively. Importantly, esters of the hydroxy ketone tautomer **128a** could be prepared in good yield. A more detailed investigation of the hydrolysis of **127** was undertaken. On

standing in $CDCl_3$ solution, **127** quantitatively isomerized into **132** within 3 days (presumably catalyzed by adventitious HCl); molecular mechanics[a] indicated that **132** was 2.1 kcal/mol more stable than **127** largely due to the decreased steric interaction between the C-11 methyl group with H_2C-1 in the former. Hydrolysis of **132** (10% aq. HCl in THF, 14 days) also gave **131** but much more slowly than hydrolysis of **127** (14 h) under the same conditions.

Scheme 21



(a) i. Ph_2PCl, pyridine, toluene. ii. I_2; (b) H_2, Pd-C (65% from **128**); (c) i. NaOH, MeOH, reflux; ii. NMO, TPAP (85%); (d) i. Tf_2O, 2,6-di tert-butyl-4-methylpyridine; ii. Bu_3SnH, LiCl, $Pd(Ph_3P)_4$, THF (50%); (e) i. $NaN(TMS)_2$, THF, -78°C; ii. $PhNTf_2$; iii. CO, DIEA, $Pd(Ph_3P)_4$, THF (50%); (f) DIBAL-H (50%); (g) 1 N $HClO_4$, THF (80%).

Exposure of **127** to DCl in CD_3OD solution gave **130** at the same rate as the loss of **127** suggesting the formation of **129** as an intermediate (**Scheme 20**). The formation of **130** indicated that hydrolysis of **127** without

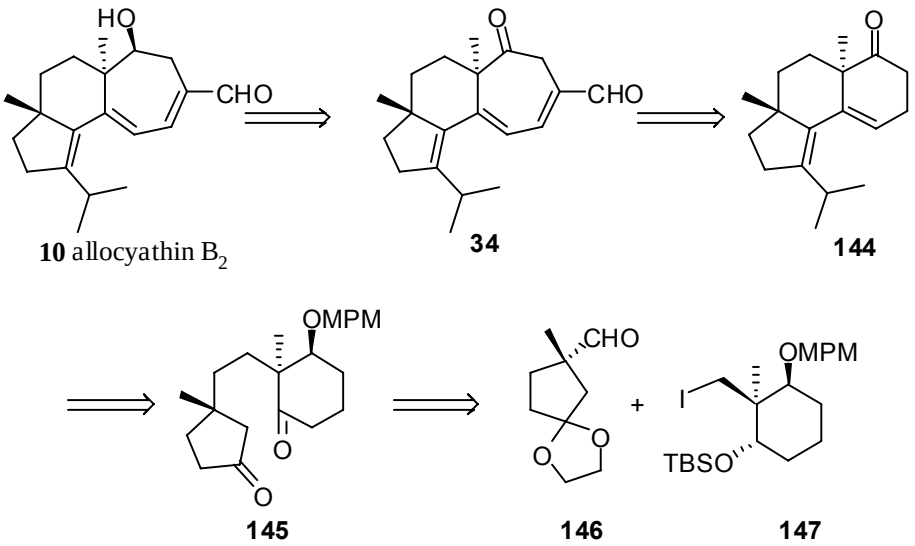
[a] CaChe version 3.9.

isomerization to **131** might be possible. After considerable experimentation, it was found that reaction of **127** with pyridinium 4-methylbenzenesulfonate (PPTS) in aqueous acetone for 12 days gave **128** (80%) along with recovered **127** (15%) (**Scheme 20**). The key intermediate **128** has a functionality that could potentially provide access to any of the various oxidation patterns present on the ring-A of cyathin and related diterpenes.

The remainder of the synthesis was done on a small scale without optimization of the reaction conditions. Deoxygenation[55] of the C-19 alcohol group was accomplished by reaction of **128** with Ph_2PCl followed by I_2 and reduction of resulting iodide **140** with H_2 over Pd-C to give **141** (**Scheme 21**). Treatment of **141** with NaOH in MeOH served to hydrolyze the benzoate ester with concomitant isomerization of the C-4,5 double bond into the required conjugated position. This isomerization reestablished the desired *trans* 6-7 ring fusion. The resulting alcohol was directly oxidized to ketone **102** with NMO and TPAP.[56] Selective deoxygenation of the cyclopentenone carbonyl was achieved by reaction of **102** with triflic anhydride in the presence of a hindered base to give the dienol triflate,[57] which was reduced[58,59] to cyclopentadiene **142** by Pd-catalyzed reduction with Bu_3SnH. Finally, introduction of the vinyl hydroxymethyl group was achieved by Pd-catalyzed carbonylation[60] of the vinyl triflate derived from **142** followed by DIBAL-H reduction of the resulting ester **143** to give **39**. Hydrolysis of **39** to racemic allocyathin B_3 (a mixture of hydroxy ketone and hemiacetal tautomers) proceeded readily in THF solution on exposure to aqueous $HClO_4$.

1.4.5 Nakada's synthesis

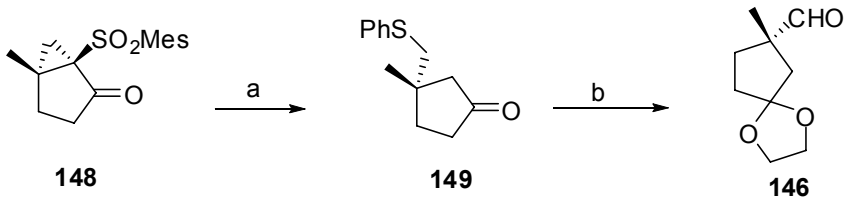
Scheme 22



10 allocyathin B_2 **34** **144** **145** **146** **147**

Nakada[61] recently reported the total synthesis of (+)-allocyathin B_2, the first enantioselective synthesis of a cyathane diterpene. The general features of Nakada's synthesis are outlined retrosynthetically in Scheme 22. The key steps involved an intramolecular aldol reaction, a samarium diiodide-mediated ring-expansion as previously adopted by Piers,[37] and a one-pot iodination-elimination to introduce the C-11,12 olefin.

Scheme 23



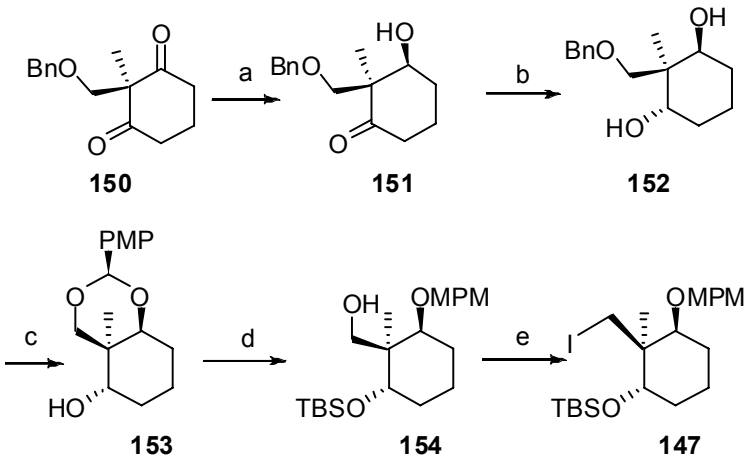
148 **149** **146**

(a) i PhSH, *t*-BuOK, *t*-BuOH 35°C, 10h, 99%; ii Lithium naphthalenide THF, -78°C, 30 min, 86%; (b) i ethylene glycol, $CH(OEt)_3$ PTSA, CH_2Cl_2, rt, 4h, 91%; ii *m*-CPBA, CH_2Cl_2, -40°C, 1h, quant; iii TFAA, TEA, rt, 3h, 87%.

Nakada began with synthesis of the chiral building blocks **146**[62] and **147**[63].

PhSH mediated ring opening of cyclopropane **148** followed by reductive removal of the sulfone gave ketone **149** (**Scheme 23**). Straightforward functional group manipulation on **149** gave the desired **146** in two steps.

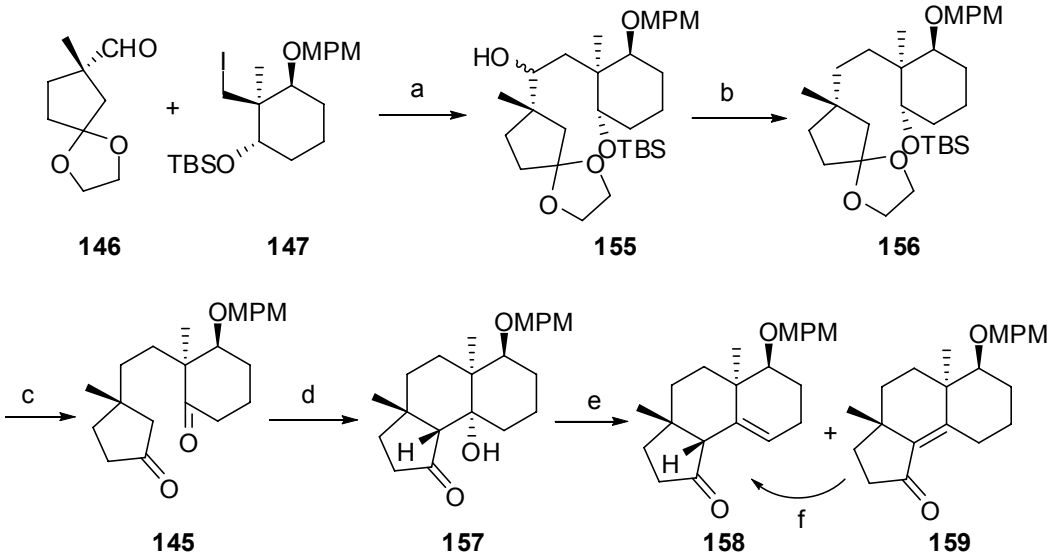
Scheme 24



(a) baker's yeast; (b) $Me_4NH(OAc)_3$; (c) i H_2, Raney-Ni, rt, 12h, quant; ii p-MeOPhCH$(OMe)_2$, CSA CH_2Cl_2, rt, 2h, 90% (d) i TBSOTf, DIPEA rt, 1h, quant; ii DIBAL-H, hexane rt, 4h, 97% (e) PPh_3, I_2 imidazole benzene reflux overnight, 93%.

Chemoenzymatic reduction of the readily available **150** with baker's yeast,[63] followed by $Me_4NH(OAc)_3$ reduction gave diol **152** (**Scheme 24**). The three oxygens in **152** were fully differentiated in four steps to provide **154** that was easily converted into the desired iodide **147**.

Scheme 25



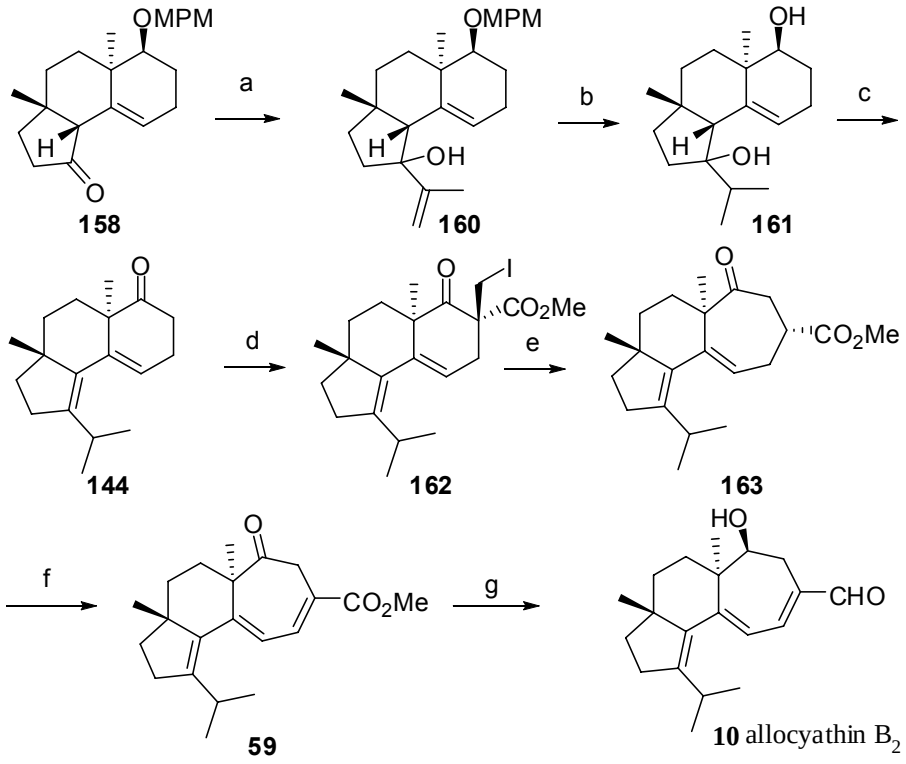
(a) *t*-BuLi -78°C Et_2O/THF (10:1); Fragment A -78°C to rt 79%; (b) i NHMDS, CS_2, MeI, rt, 10h, 91%; ii *n*-Bu_3SnH, AIBN (cat), toluene reflux, 2h, 89%; (c) i 2NHCl/THF(1:2) 50°C, 11h, quant; ii Dess-Martin periodinane CH_2Cl_2, rt, 1h, 93%; (d) *t*-BuOK benzene 0°C to rt 2h, 94% (e) $SOCl_2$ Py CH_2Cl_2 0°C to rt 2h; (f) 2-bromopropene, *t*-BuLi, Et_2O, -78°C 1h, 72%.

After halogen-metal exchange, fragment **147** was coupled with fragment **146** to furnish **155** as a mixture of diastereomers (**Scheme 25**). Deoxygenation of **155** was achieved by tinhydride reduction of the corresponding methyl xanthate to give **156**. Removal of the silyl ether and ethylene acetal protecting groups in **156** followed by Dess-Martin oxidation provided the diketone **145**. Intramolecular aldol reaction of **145** was achieved in an aprotic solvent to furnish **157**. Dehydration of **157** gave a separable mixture of **158** and **159**. Treatment of **159** with base isomerizes the C-4,5 double bond into the required position to provide **158**.

Reaction of **158** with isopropenyllithium gave **160** (**Scheme 26**). Subjecting **160** to hydrogenation served to remove the MPM group with concomitant reduction of the isopropenyl double bond. Dess-Martin oxidation of the resulting alcohol **161** followed by dehydration gave a mixture of

regioisomeric alkenes. This mixture was isomerized to the desired conjugated diene **144** by refluxing in benzene in the presence of p-TsOH.

Scheme 26



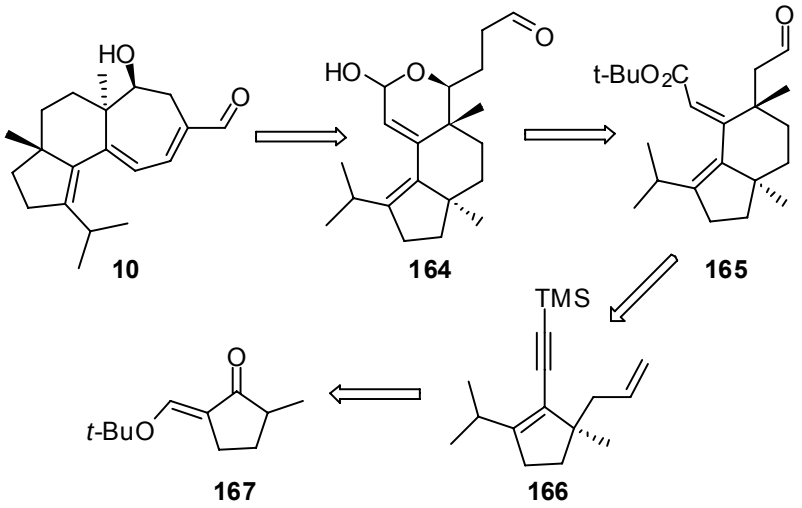
(a) 2-bromopropene *t*-BuLi, Et_2O -78°C, 1h 72%; (b) H_2 (1atm) Pd/C MeOH rt, 6h, 96%; (c) i Dess-Martin periodinane CH_2Cl_2, rt overnight, 92%; ii $SOCl_2$, Py CH_2Cl_2 0°C to rt 2h, 90%; iii PTSA, C_6H_6 reflux, 6h 85%; (d) i LHMDS, $NCCO_2Me$ THF, -78°C, 0.5h, 87%; ii CH_2I_2, TBAF, THF 0°C to rt, 0.5 h, 86%; (e) SmI_2, HMPA THF, -78°C, 10 min, 91%; (f) i LDA (5 eq), THF -78°C to 0°C, 1h; ii I_2 (2 eq) THF, -78°C to 0°C, 1h, 71%; (g) i $LiAlH_4$, Et_2O, -78°C 10 min, 89%; ii MnO_2, CH_2Cl_2, rt 12h, 90%.

Conversion of **144** to the corresponding β-keto ester[64] was followed by iodomethylation to provide **162** as the key intermediate for ring expansion (**Scheme 26**). Samarium diiodide-mediated ring expansion of **162** furnished **163** with the desired 5-6-7 tricyclic system. The C-11,12 double bond was introduced by a one-pot[65-67] operation, which involved treatment of **163** with

excess LDA followed by I_2 to give **59**. Global reduction of the ketone and the ester in **59** followed by selective oxidation of the resultant allylic alcohol by the known protocol completed the total synthesis of (+)-allocyathin B_2.

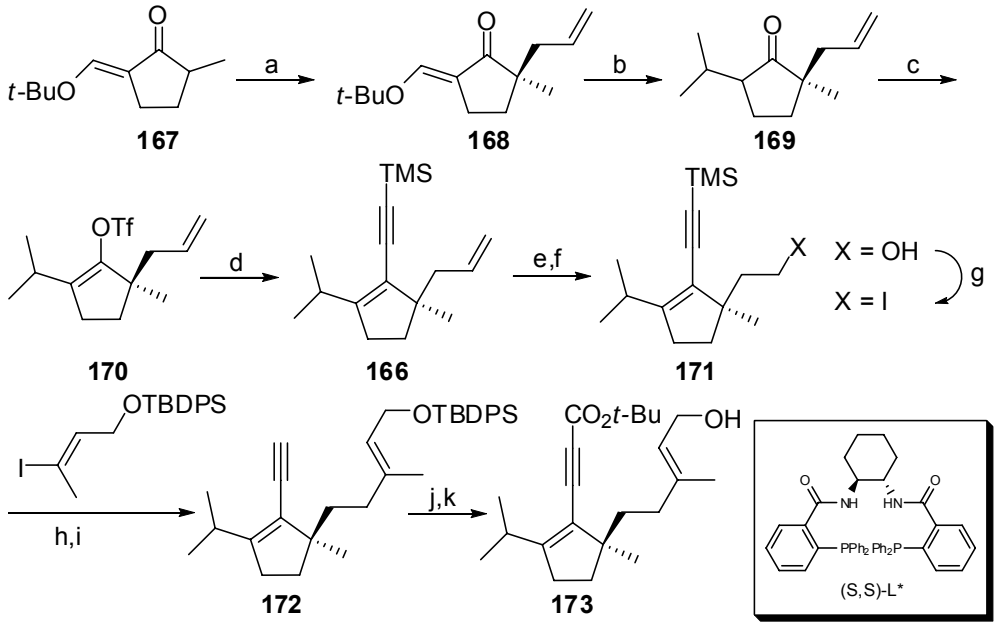
1.4.6 Trost's synthesis

Scheme 27



The enantioselective synthesis of allocyathin B_2 by Trost[68] is based on a strategy that takes advantage of the palladium-catalyzed asymmetric allylic alkylation[69,70] of prochiral ketone enolates (**Scheme 27**). The six-membered B ring was prepared through a transition metal-catalysed cycloisomerization. The assembly of the highly functionalized seven-membered ring was deferred to the last stage in the synthesis via an aldol cyclization.

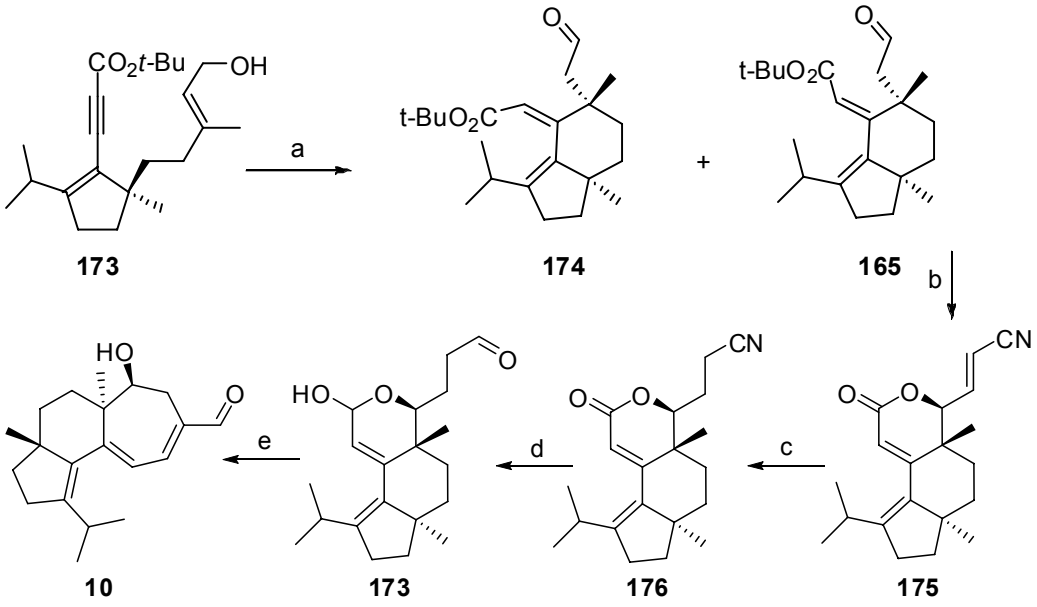
Scheme 28



(a) LDA, $[(\eta^3\text{-}C_3H_7)PdCl]_2$ (0.5 mol %), (S,S)-L* (1 mol %), allylacetate, Me_3SnCl, *t*-BuOH, 83%, 95% ee; (b) Me_2CuLi, -20°C to room temperature, 86%; (c) LDA, $PhNTf_2$, 96%; (d) $Pd_2(dba)_3CHCl_3$ (2.5 mol %), PPh_3 (20 mol %), CuI (5 mol %), TMS-acetylene, $BuNH_2$, 50°C, 85%; (e) OsO_4 (1 mol %), NMO; $NaIO_4$, 87%; (f) $NaBH_4$, 94%; (g) PPh_3, I_2, ImH, 97%; (h) *t*-BuLi, $ZnCl_2$, -78 °C to room temperature, then $Pd(PPh_3)_4$ (5 mol %), **12**; (i) K_2CO_3, MeOH, 74% from **11**; (j) n-BuLi, $(Boc)_2O$, -78°C to room temperature, 99%; (k) TBAF, 52-55%.

The synthesis commenced with asymmetric allylic alkylation of **167**[71] followed by addition of lithium dimethylcuprate (**Scheme 28**). Subjecting the resulting ketone **169** to triflation followed by a Sonogashira coupling[72] reaction generated the enyne **166**. The further elaboration of the Z-alkene was accomplished by oxidative cleavage of the allyl side chain followed by reduction, iodination and a Negishi coupling[73,74] reaction and monodesilylation to provide the alkyne **172**. The straightforward acylation and deprotection of **172** provide the ynoate **173** which is ready for the pivotal cycloisomerization to construct the six-member B ring.

Scheme 29



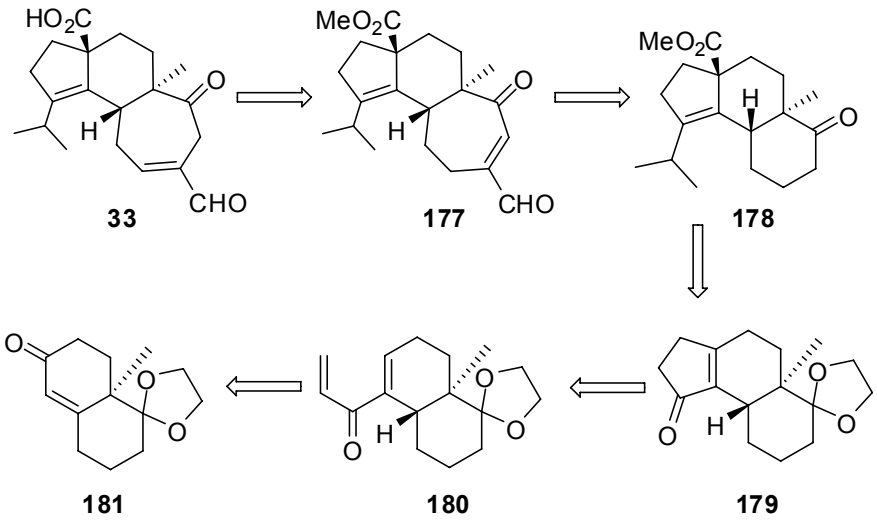
(a) 20 mol % $CpRu(CH_3CN)_3PF_6$,100 mol % DMF, 2-butanone (0.1 M), rt, 55%; (b) $PhS(O)CH_2CN$, piperidine, 75%; (c) 10% Pd/C, H_2, 83%; (d) DIBAL-H; (e) KOH, MeOH, 60 ^oC, 51% from **176**.

The key metal-catalyzed cycloisomerization of 1,6-enynes was investigated with both palladium and ruthenium[75-78] catalysts (**Scheme 29**). Eventually, the Ru-catalyzed cycloisomerization of the **173** gave compound **165** in 48% yield as a single diastereomer. The aldehyde substituent of **165** was extended via a hydroxylative Knoevenagel reaction[79-81] to generate the lactone **175**. Selective hydrogenation of **175** followed by a DIBAL-reduction set the stage for the construction of the seven-membered C ring. The intromolecular aldol condensation of the aldehyde **173**, similar to the Tori route,[33] completed the synthesis of **10** in 19 steps from 2-methyl cyclopentanone.

1.4.7 Danishefsky's synthesis

Danishefsky's[82] asymmetric total synthesis of a member of this cyathane sub-family scabronine G is the first synthesis of this class of tricyclic diterpenoids. The general features of Danishefsky's synthesis are outlined retrosynthetically in **Scheme 30**. The key steps involved Nazarov[83] cyclization of divinyl ketone **180** to assemble the A ring**,** stereoselective Nagata addition to introduce the isopropyl group and C-17, and the $HgCl_2$ mediated ring expansion of **178** to construct the seven-membered C ring.

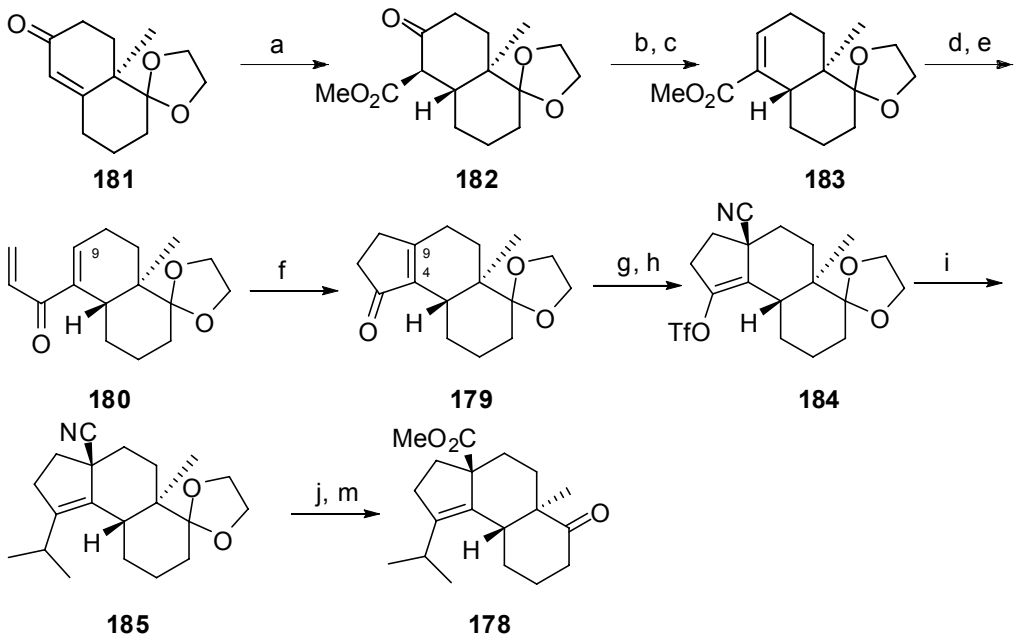
Scheme 30



The synthesis commenced with the dissolving metal reduction of enone **181** and acylation of the resulting enolate with Mander's reagent[84] to provide the ketoester **182** (**Scheme 31**). Subsequent enol triflation and hydride reduction[59] of **182** afforded the ester **183**. Addition of vinylmagnesium bromide to the corresponding Weinreb amide[85] of **183** generated the divinyl ketone **180**. The desired cyclopentenone **179** was prepared as a single isomer via a Lewis acid-mediated Nazarov cyclization of **180**. An axial

conjugate addition of a cyanide nucleophile[86] to **179** was envisioned through stereoelectronic principles. Trapping the enolate[87] resulting from cyanide addition to **179** as its triflate followed by Negishi coupling gave **185** with the isopropyl group installed at the C-2 position. Reduction of the nitrile in **185** followed by oxidation, methylation and deketalization generated the cyclohexanone **178**.

Scheme 31

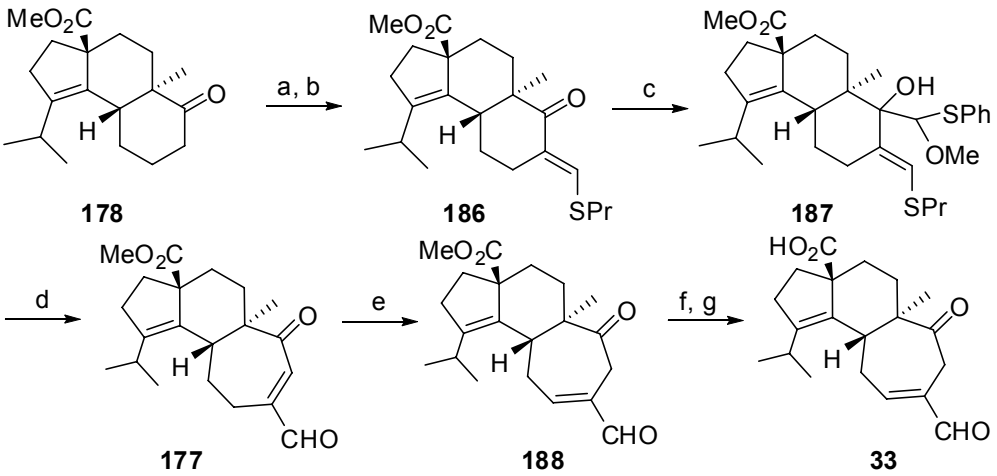


(a) Li/NH_3, t-BuOH, THF, -78 °C; $NCCO_2Me$, 72%; (b) NaH, $PhNTf_2$, DME, 98%; (c) $Pd(PPh)_3$, Bu_3SnH, LiCl, THF, 55 °C, 91%; (d) LHMDS, Me(OMe)NH,HCl, THF, -10 °C, 79%; (e) vinylMgBr, THF, -10 °C, 84%; (f) $FeCl_3$, CH_2Cl_2, 72%; (g) Et_2AlCN, THF, Et_3N, TMSCl; (h) *t*-BuOK, THF, -78 °C, N-(5-chloro-2-pyridyl)triflimide, 86% over two steps; (i) *i*-PrMgCl, $ZnCl_2$, LiCl, (dppf)$PdCl_2$, THF, 55 °C, 75%; (j) DIBALH, CH_2Cl_2, -78 °C, 88%; (k) $NaClO_2$, NaH_2PO_4, *t*-BuOH/H_2O; (l) MeI, K_2CO_3, DMF; (m) THF, HCl/H_2O; 92% over three steps.

Conversion of the cyclohexanone **178** to the thiopropylmethylidene intermediate **186** was achieved in two straightforward steps (**Scheme 32**). Subsequent addition of lithiated methoxymethylphenyl sulfide gave alcohol

187 and set the stage for the pivotal rearrangement step. The $HgCl_2$-mediated ring expansion[88] of **187** followed by isomerization of the double bond afforded scabronine G methyl ester **188**, that was hydrolyzed to provide the natural product **33** after chemoselective protection of the aldehyde group.

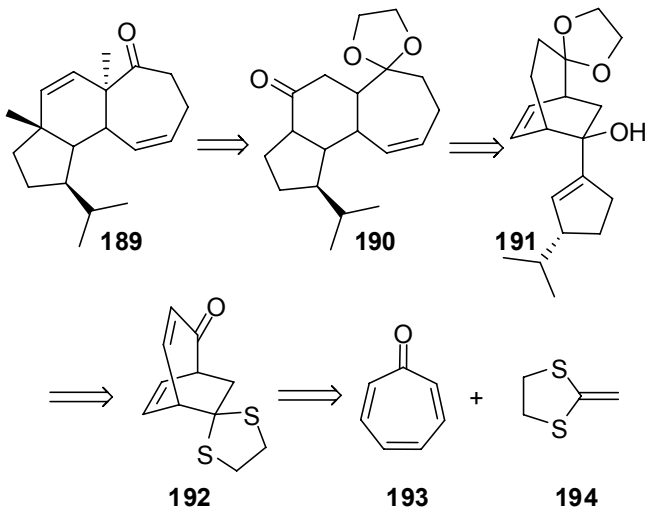
Scheme 32



(a) NaH, HCO_2Me, DME, 97%; (b) n-PrSH, TsOH, PhH, 50 °C, 93%; (c) n-BuLi/$MeOCH_2SPh$, THF, -78 °C; (d) $HgCl_2$, HCl/MeCN, 80 °C, 86% over two steps; (e) DBU, benzene, 75 °C, quant; (f) TsOH, $HO(CH_2)_2OH$, PhH, 89%; (g) aq. NaOH, MeOH, 55 °C, then HCl, 87%.

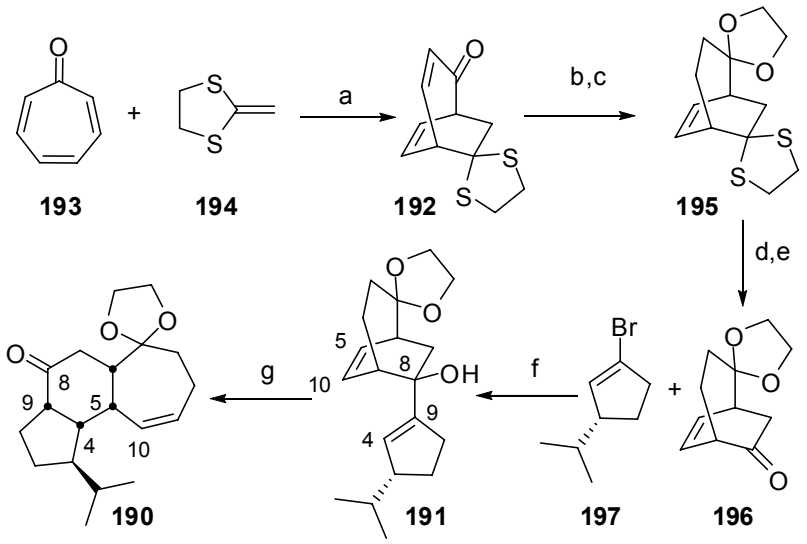
1.4.8 Paquette's approach

Scheme 33



Dahnke and Paquette[89] reported a synthetic approach to cyathanes which rapidly provided enantiopure ketone **190**. The general features of Paquette's approach are outlined retrosynthetically in **Scheme 33**. The key steps involved an inverse electron demand Diels-Alder reaction to introduce the seven-membered C-ring, a sigmatropic rearrangement to furnish the 5-6-7 tricyclic system, and Johnson's sulfoxime resolution to arrive at enantiopure ketone **196**.

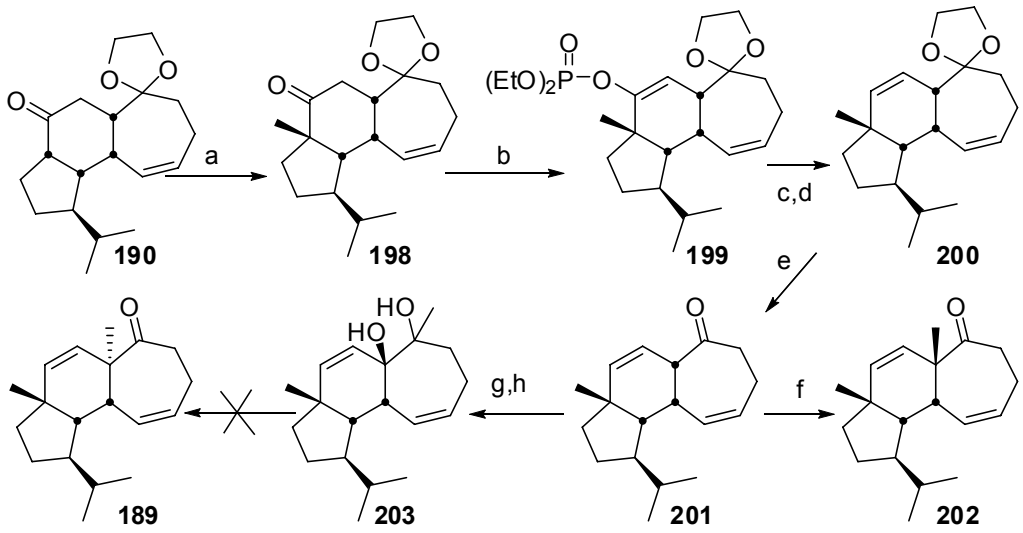
Scheme 34



(a) cat. Et_3N, 120°C, 56%; (b) DIBAL-H, MeCN, HMPA, THF, 92%; (c) $HO(CH_2)_2OH$, p-TsOH, 98%; (d) chloramine-T, acetone, aq. MeOH, 56%; (e) Johnson's sulfoxime resolution, 87%; (f) ^{t}BuLi, **A**, 51%; (g) KH, 18-crown-6, THF, 90°C, 83%.

Paquette's synthesis commenced with an inverse electron demand Diels-Alder reaction between tropone and dithioketene acetal **194** to provide **192** (**Scheme 34**). Selective reduction of the resulting enone followed by protecting group manipulation yielded ketone **196**. Ketone **196** was resolved via Johnson's sulfoxime method. The key intermediate **191** was prepared by direct addition of the enantiopure organolithium reagent derived from (-)-**197** to **196**. Subjecting the resulting alcohol **191** to potassium hydride in the presence of 18-crown-6 generated the corresponding oxyanion, which triggered an oxy-Cope rearrangement to furnish **190** with the desired 5-6-7 tricyclic ring system. This transformation served to close the B-ring by forming the C4-C5 bond with concomitant fragmentation of the bicyclic system to unmask the C-ring by breaking the C8-C11 bond.

Scheme 35



(a) KH, MeI, THF, 87%; (b) LHMDS, $CIP(O)(OEt)_2$, THF, 87%; (c) H_2, PtO_2, 90%; (d) Li, $EtNH_2$, EtOH, Et_2O, 95%; (e) HCl, THF, 57%; (f) KH, MeI, THF, 59%; (g) KHMDS, $(TMSO)_2$, THF, 46%; (h) MeMgBr, THF, 99%.

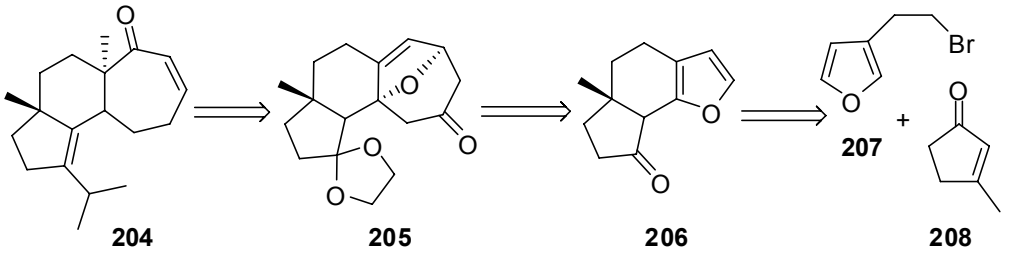
With the tricyclic system **190** in-hand, the stage was set for the installation of the *trans*-methyl groups at C6 and C9. Direct methylation of enolate **190** under thermodynamic control selectively yielded the desired isomer **198** (**Scheme 35**). The face selectivity of this reaction is governed by the concave shape of **190**. However, this also makes addtion of the C-6 methyl group from the opposite face difficult, and gave the wrong stereoisomer **202**. An indirect method via pinacol rearrangement was also attempted but without success.

1.4.9 Wright's approach

Wright[90] reported a synthetic approach to cyathanes, that rapidly furnished the 5-6-7 tricyclic system. The general features of Wright's approach are

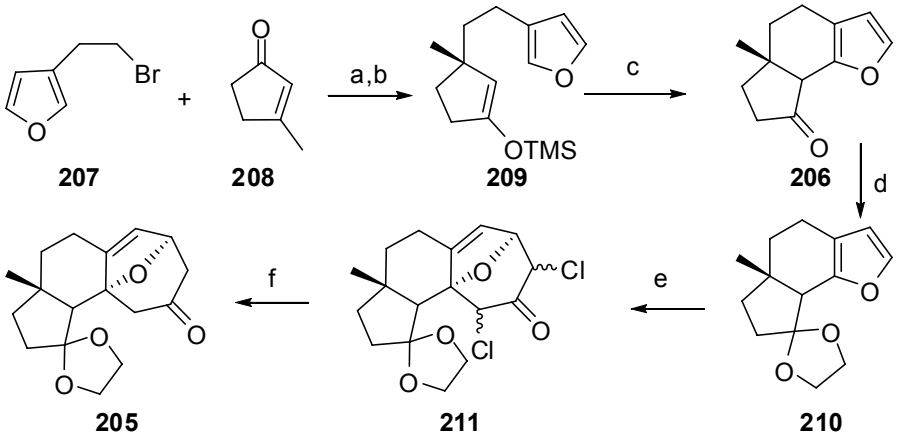
outlined retrosynthetically in **Scheme 36**. The key steps involve an electrochemical mediated furan annulation[91-93] and an intermolecular 4C+3C cycloaddition[94-97] on the annulated furan. Wright's approach targeted the advanced intermediate **204**, which could be a potential precursor to a variety of cyathins. Wright envisioned that compound **204** could be derived from the oxo-bridged tricycle **205**.

Scheme 36



Wright's approach began with cuprate addition to 3-methylcyclopentenone **208** and trapping the enolate with TMSCl as silylenol ether **209** (**Scheme 37**). The cuprate was generated from **207**[98] *in situ* via the Grignard reagent. Subjecting **209** to electrochemical oxidation closed the six-membered B-ring, providing the tricyclic furan **206** as a single isomer. Reaction of the derived acetal **211** with the oxyallyl cation generated from 1,1,3-trichloroacetone and sodium trifluoroethoxide gave **211** with high face selectivity. Reductive dechlorination of **211** provided **205,** the most advanced structure reported from this approach to date. Although **205** has the complete 5-6-7 ring system, further elaboration is still required; i.e. the methyl group at C-6, the isopropyl group at C-3, the *trans* 6-7 ring fusion, and extensive oxygenation needed to complete the cyathane skeleton.

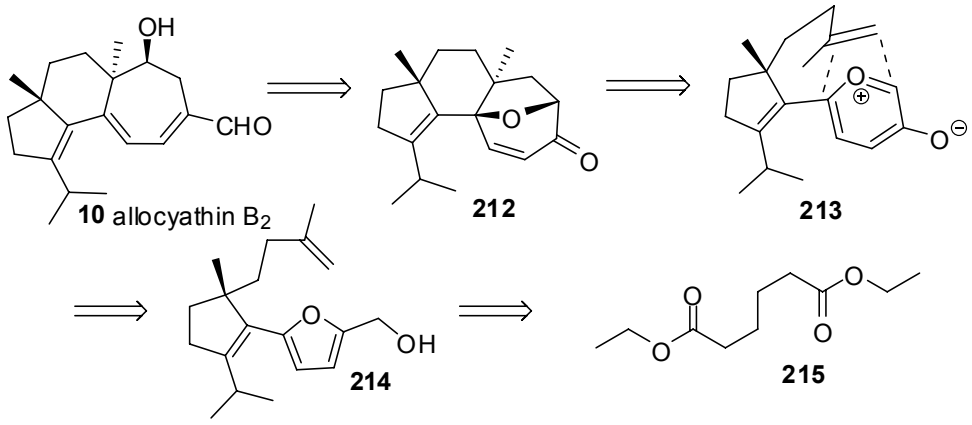
Scheme 37



(a) Mg, THF; (b) CuI, TMSCl, Et_3N, -78°C to r.t; (c) anodic oxidation, MeCN, ^{i}PrOH, $LiClO_4$, 2,6 lutidine, 65%; (d) p-TsOH, $HO(CH_2)_2OH$, $CH(OEt)_3$, 85%; (e) 1,1,2 trichloroacetone, $NaOCH_2CF_3$, CF_3CH_2OH; (f) Zn-Cu couple, NH_4Cl, MeOH, 75% 2 steps.

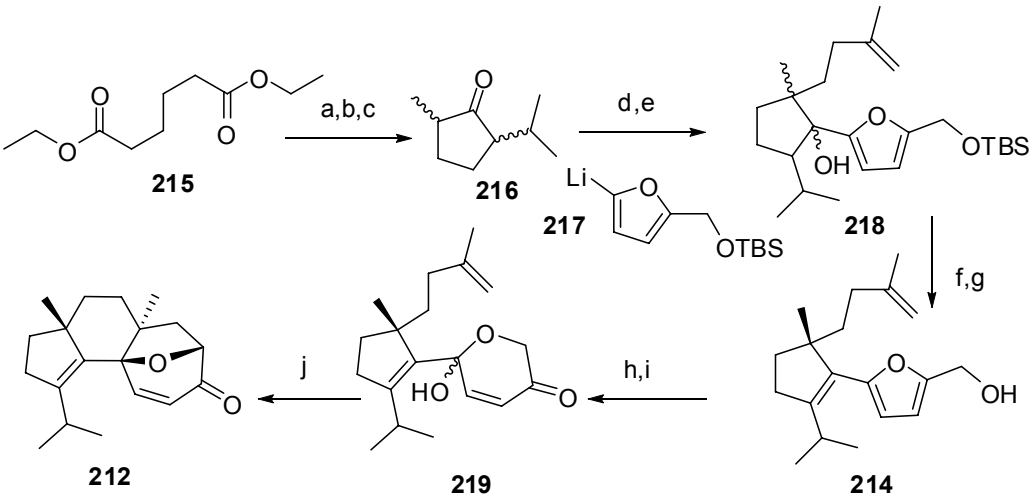
1.4.10 Magnus' approach

Scheme 38



Magnus[99] developed an elegant approach for rapidly providing the 5-6-7 tricyclic system with 1,4-*anti* methyl groups as present in the cyathanes. The general features of Magnus' approach are outlined retrosynthetically in **Scheme 38**. The key step involved oxidative rearrangement of a furylmethanol to provide the precursor for an intramolecular pyrylium ylide-alkene [5+2] cyclization[100-105] to furnish both the B and C ring in one operation. Magnus' synthesis commenced with a Dieckmann cyclization of diethyl adipate. Methylation of the resulting keto ester followed by decarboxylation yielded ketone **216** (**Scheme 39**).

Scheme 39



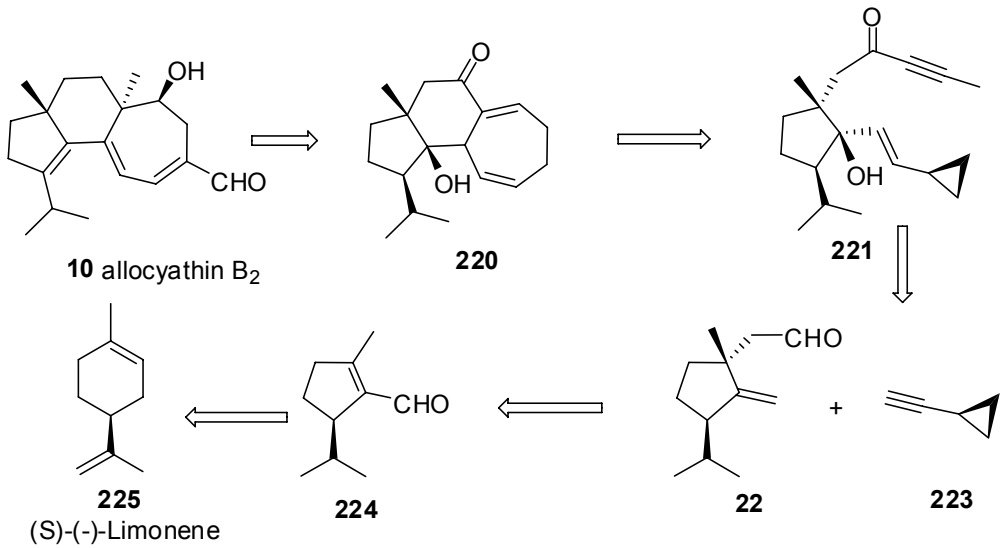
(a) KOEt, 2-iodopropane; (b) NaOEt, MeI, Toluene; (c) H_2SO_4, H_2O, reflux; (d) LDA, THF, 4-iodo-2-methyl-1-butene, 53%; (e) $CeCl_3$, A, 90%; (f) $SOCl_2$, pyridine, 94%; (g) CsF, 97%; (h) O_2, hv, rose bengal; (i) Me_2S; (j) TFA, DCM, 62% 3 steps.

Regioselective alkylation of the enolate of **216** followed by addition of the 2-lithiofuran derivative **217** gave **218** as a mixture of isomers. Dehydration of this mixture of alcohols followed by deprotection gave **214**. Subjecting **214** to William's oxidative rearrangement[106] protocol provided the desired precursor **219**. Treatment of **219** with TFA generated the transient dipolar intermediate, which triggered the intramolecular [5+2] cycloaddition[107] and arrived at **212**. Further elaboration of the C-ring is still required to complete the synthesis of cyathane skeleton.

1.4.11 Wender's approach

Wender[108] reported an approach toward (+)-allocyathin B_2 starting from commercially available (S)-(-) limonene. The general features of Wender's approach are outlined retrosynthetically in **Scheme 40**. The key step involved an intramolecular [5 + 2] cycloaddition to assemble the B and C-rings in one operation.

Scheme 40



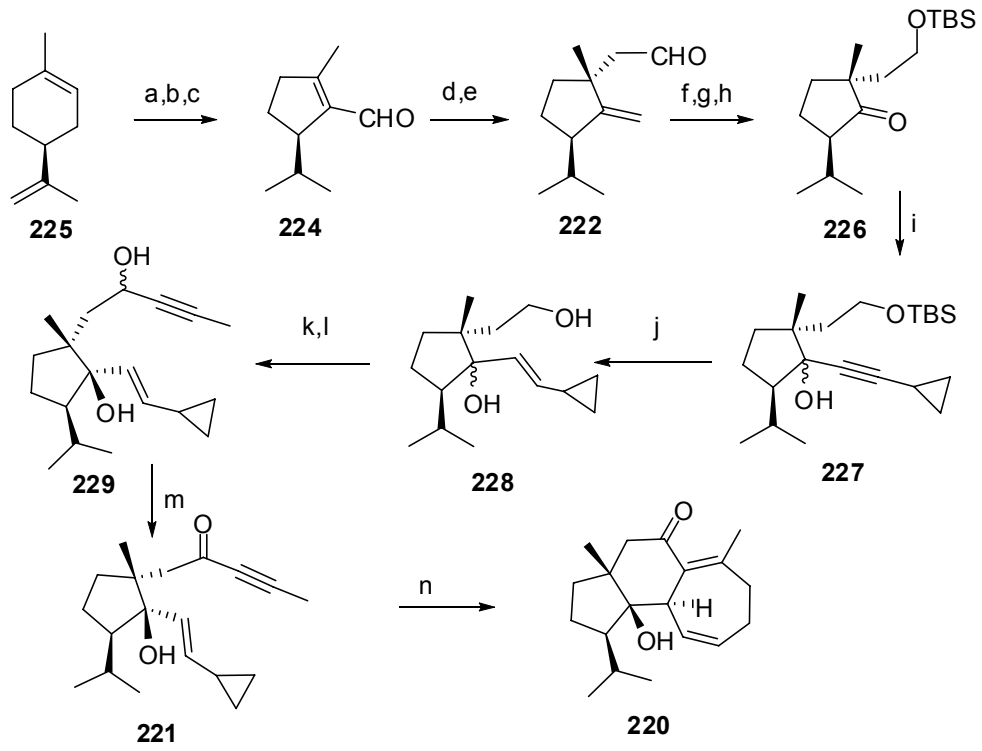
10 allocyathin B_2 **220** **221**

225 (S)-(-)-Limonene **224** **22** **223**

Wender's approach started with enantiopure **224** prepared from (S)-(-)-limonene by chemselective hydrogenation, Johnson-Lemieux oxidation, and intramolecular aldol (**Scheme 41**). DIBAL-H reduction of the enal **224** followed by vinyl ether formation and Claisen rearrangement gave aldehyde **222** as the major isomer. Aldehyde **222** was reduced and the resulting alcohol protected as a tert-butyldimethylsilyl ether followed by ozonolysis to afford the ketone **226**. Reaction of **226** with the organocerium reagent prepared from cyclopropylacetylide followed by selective reduction of alkyne **223** provided **227** with the vinylcyclopropane installed. Deprotection of the primary alcohol in **227** and subsequent Dess-Martin oxidation, Grignard addition, and oxidation gave the key precursor **221**.

Subjecting **221** to Rh-catalyzed [5 + 2] cycloaddition protocol gave the cycloadduct **220** in good yield. Several key transformations remain to be established if **220** is to be used as a precursor for the synthesis of a cyathane diterpene.

Scheme 41

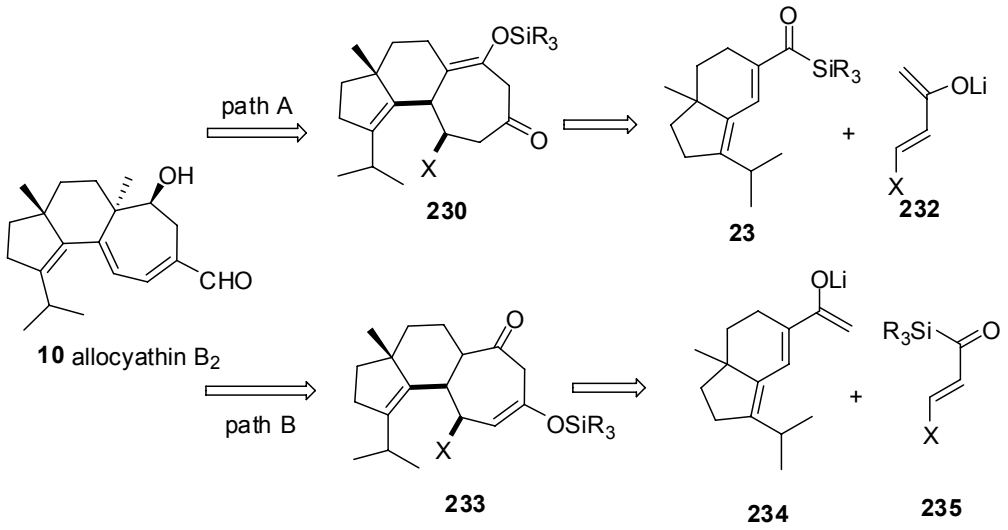


(a) H_2, PtO_2, 94%; (b) 1 mol % OsO_4, $NaIO_4$, THF/H_2O, 97%; (c) piperidine, AcOH, PhH, 75%; (d) DIBAL-H, Et_2O, 0 °C, 96%; (e) $EtOCH=CH_2$, $Hg(OAc)_2$, then $PhCH_3$, 90%; (f) $NaBH_4$, MeOH/H_2O, 95%; (g) TBSCl, imidazole, DMF, 90%; (h) O_3, CH_2Cl_2, -78 °C, Me_2S, 65%; (i) 1-ethynylcyclopropane, n-BuLi, $CeCl_3$, 0 °C, 91%; (j) $LiAlH_4$, MeONa, THF, 69%; (k) DMP, $NaHCO_3$, CH_2Cl_2; (l) MeCCMgBr, THF, 75% over two steps; (m) DMP, $NaHCO_3$, CH_2Cl_2, 93%; (n) 5 mol % $[Rh(CO)_2Cl]_2$, 1,2-dichloroethane (0.02 M), 80°C, 3.5 h, 90%.

1.4.12 Takeda's approach

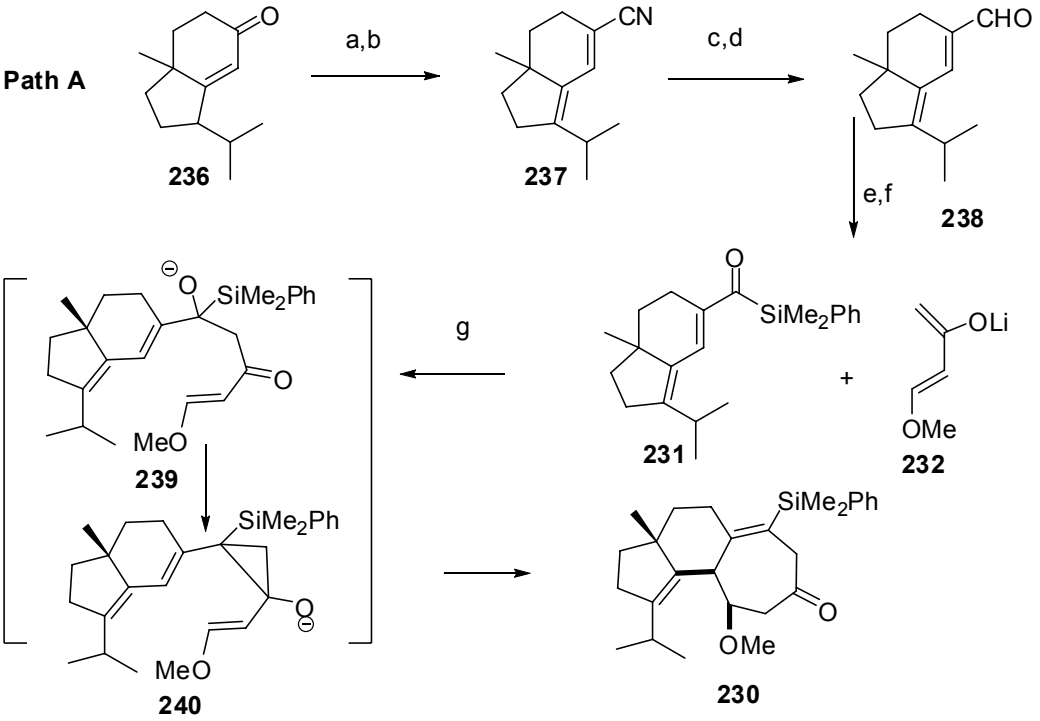
Takeda[109] developed an approach toward allocyathin B_2, outlined retrosynthetically in **Scheme 42**. The key step involved a Brook rearrangement-mediated [3 + 4] annulation.[110-113] Two retrosynthetic pathways have been addressed based on this transformation.

Scheme 42



Path A commenced with ZnI_2 catalyzed nitrile addition followed by $POCl_3$ mediated elimination to provide **237** (**Scheme 43**). Quenching the DIBAL-H reduction of **237** with an acid yielded aldehyde **238**. Sequential dimethyl(phenyl)silyllithium addition[114] and TPAP oxidation converted **238** into the desired acylsilane. Treatment of **255** with the lithium enolate of 4-methoxy-3-buten-2-one (**231**) gave the 1,2-adduct **239**, which underwent a Brook rearrangement to **240** triggering the anionic oxy-Cope rearrangement to furnish **230**.

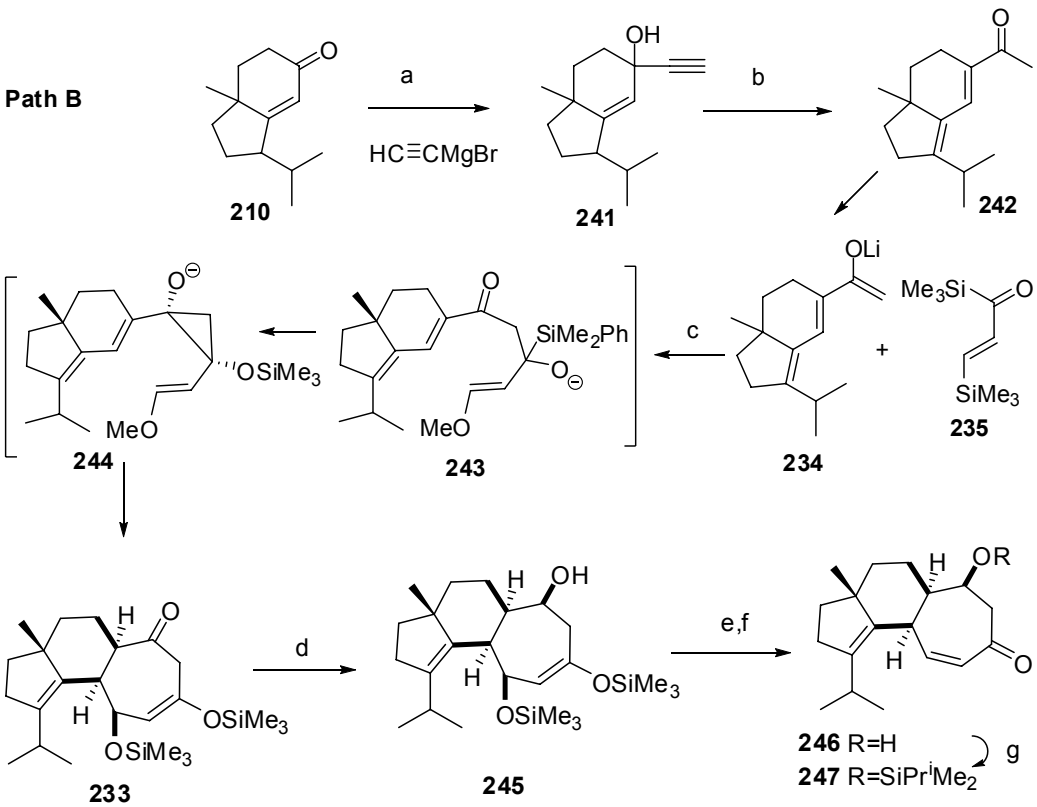
Scheme 43



(a) Me_3SiCN, ZnI_2; (b) $POCl_3$, Py, 65% 2 steps; (c) DIBAL-H; (d) $(COOH)_2$, 76%, 2 steps; (e) $PhMe_2SiLi$, THF/HMPA, -80°C, 55%; (f) n-Pr_4NRuO_4, NMO, MS-3A, DCM, 57% (g) THF, 0°C to rt.

Path B started with Grignard addition of ethynylmagnesium bromide to **210** followed by a Rupe rearrangement[115] to give bicyclic methyl ketone (**Scheme 44**). Key [3 + 4] cyclization of **234** with acryloylsilane provided **233** as a single diastereomer. Enone **246** was achieved after deprotection of **245**, which was derived from DIBAL reduction of **233**.

Scheme 44



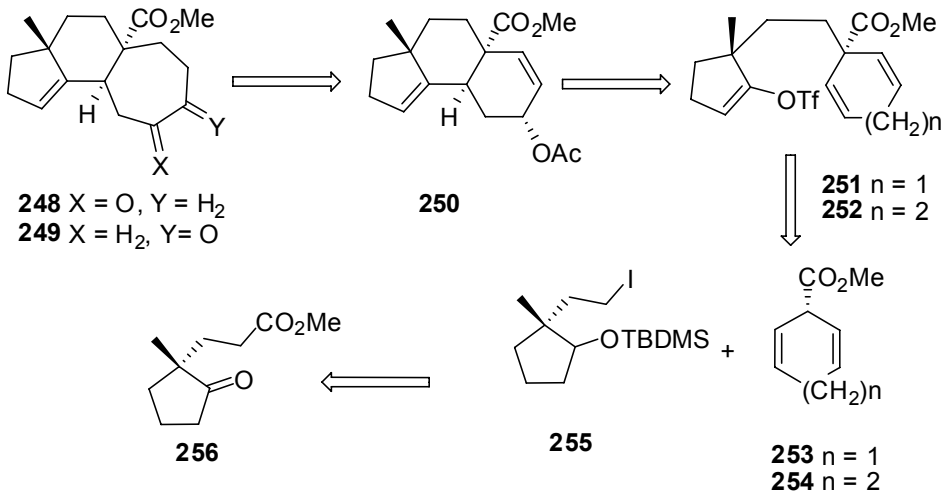
(a) THF, 0°C to rt, 92%; (b) HCO_2H, reflux, 42%; (c) THF, -80°C to 0°C; (d) DIBAL, Et_2O, -80°C, 72%; (e) NBS, THF; (f) n-Bu_4NF, 72%, 2 steps; (g) i-$PrMe_2SiCl$, imidazole, 92%.

1.4.13 Didier-Desmaële's approach

Didier-Desmaële[116,117] disclosed an approach to cyathanes starting from enantiomerically pure building block **256** (**Scheme 45**). The key step involved an intramolecular palladium-catalyzed cyclization. The original plan was to set up the cyathane ring system via a Heck-type[118] cyclization of triflate **252**. Due to the non-availability of required ester **254**, an alternative plan was adopted, requiring a one-carbon ring expansion at a

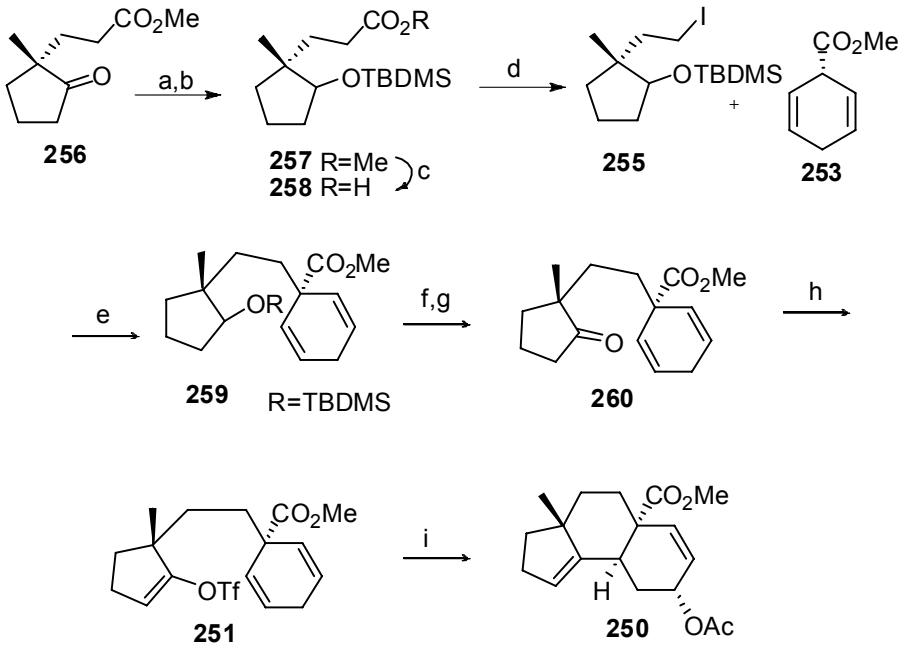
later stage.

Scheme 45



Chiral building block **256** was derived from 1-methylcyclopentanone via asymmetric Michael addition in the presence of (S)-1-phenylethylamine.[119] Treatment of **256** with sodium borohydride yield a mixture of epimeric alcohols, which were protected as TBDMS ethers (**Scheme 46**). After saponification, the corresponding acid was converted to iodide **255** through a Barton-modified Kochi reaction. DMPU mediated coupling between **253** and the lithium enolate of **255** furnished the desired diene **259**. After removal of the TBDMS group, the resulting alcohol was converted to the triflate **251** through a sequential Swern oxidation and triflation. Treatment of triflate **251** with Pd_2dba_3 in the presence of tetrabutylammonium acetate in DMSO furnished the tricyclic acetate **250**.

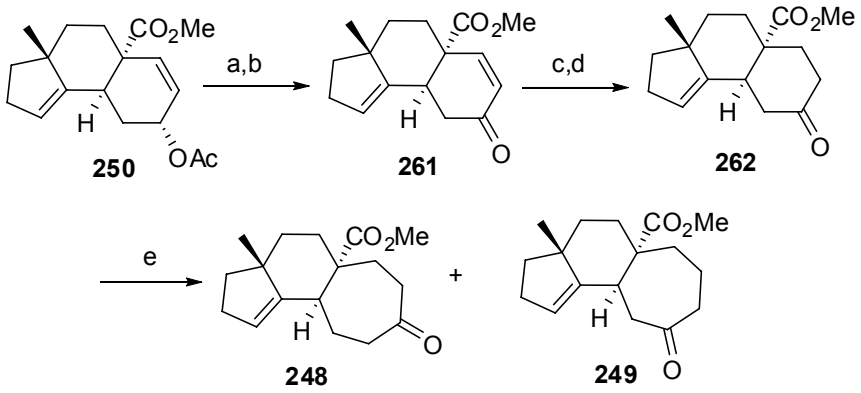
Scheme 46



(a) $NaBH_4$, MeOH, 0°C, 91%; (b) TBDMSCl, Im, DMF, 20°C, 12 h, 90%; (c) aq. KOH, MeOH, 20°C, 89%; (d) $Pb(OAc)_4$ / I_2 , 6 h, refluxing CCl_4 ; (e) i., LDA, THF, -78°C, 1 h, ii. DMPU, THF, 50°C, 3 h, 83%; (f) n-Bu_4NF, THF, 60°C, 5 h, 78%; (g) $(ClCO)_2$, DMSO, CH_2Cl_2 , -78°C, then Et_3N, 95%; (h) 2,6-di-tert-buylpyridine, Tf_2O, CH_2Cl_2 ,0°C, 79%; (i) $Pd_2(dba)_3$, n-Bu_4NOAc, LiCl, DMSO, 60°C.

With **250** in hand, the stage was then set for a one-carbon expansion of the C-ring. Installation of the C-14 hydroxyl group before the ring expansion turned out to be difficult. Saponification of the acetate in **250** followed by allylic oxidation yielded ketone **261** (**Scheme 47**). Sequential Birch reduction and oxidation of **261** provided the desired ketone **262**. Treatment of **262** with (trimethylsilyl)diazomethane in the presence of Me_3Al gave a 1.5:1 mixture of ketones **248** and **249**. Further elaboration of these ketones has not been reported.

Scheme 47



(a) MeONa, MeOH, 20°C, 3h, 96%; (b) MnO_2, toluene, 80°C, 3h, 73%; (c) Li, NH_3, t-BuOH-THF, -78°C; (d) PCC, CH_2Cl_2, AcONa, 4A sieves, 20°C, (g) i. $TMSCHN_2$, $AlMe_3$, -78 to -20°C, 3 h, ii. TFA, THF, H_2O, 78%.

1.5 Conclusion

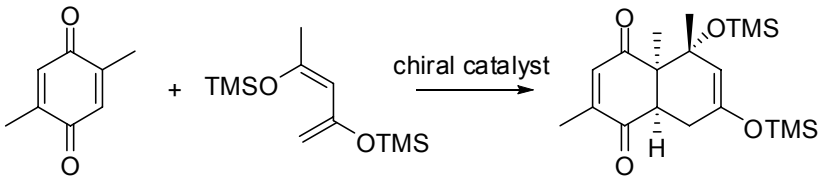
In spite of the versatile approaches that have been developed, only three of them can provide the *trans*-fused 6,7 ring system: Piers' synthesis of sarcodonin G (**26**); Danishefsky's synthesis of scabronine G (**33**) and Ward's synthesis of allocyathin B_3 (**3**). Because the *trans*-fused 6,7 ring system is one of the key structural features of the cyathin family (present in ten out of eleven cyathins), these three approaches potentially can be modified to synthesize other cyathins. Among these approaches, Danishefsky's approach is the only one that provides enantiomerically pure product by using (-)-Wieland-Miescher ketone as the starting material. Therefore, incorporating an enantioselective reaction into Ward's approach would result in a most attractive general approach toward asymmetric synthesis of cyathin diterpenes.

2. Results and Discussion

2.1 Objectives of thesis research

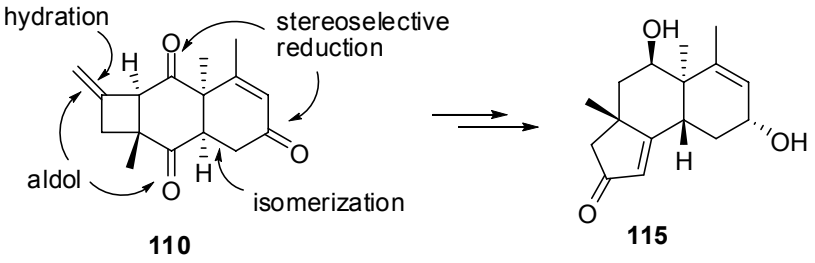
The Ward group's 1st generation synthetic approach to cyathanes culminating in (±)-allocyathin B_3 was described in section **1.4.4** (see page 20). Because the synthetic route established a trans B-C ring fusion, a fully functionalized C ring, and proceeded via intermediates having useful functionalities in the A ring and the isopropyl group, it had the potential to provide access to any of the known cyathin diterpenes. The goal of my thesis research was to establish an enantioselective 2nd generation synthetic route to cyathane diterpenes. The specific objectives for the 2nd generation synthesis were:

Objective 1: Develop an enantioselective version of the first Diels-Alder reaction.



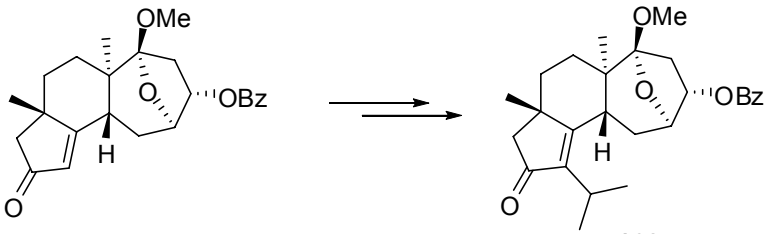
106 **105** **108**

Objective 2: Establish a more direct route from 110 to 115.



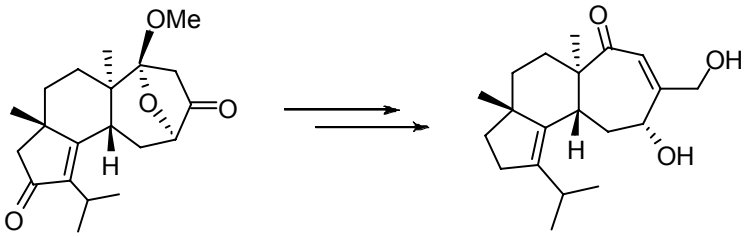
110 **115**

Objective 3: Develop a more direct approach to introduce the isopropyl group.



103 **102**

Objective 4: Establish a synthetic route to cyathin A_3



102 **cyathin A_3**

2.2 Enantioselective quinone Diels-Alder reactions

2.2.1 Introduction

Diels-Alder reactions with a quinone as the dienophile are a powerful method to construct functionalized *cis*-fused decalin systems, and have been applied to many syntheses of complex natural products.[120] However, general methodology for conducting the key quinone Diels-Alder reaction enantioselectively is not yet available. In most examples, the initial Diels-Alder reaction generated a racemic adduct from which the synthesis of an enantiomerically pure natural product can only be achieved with a resolution step.

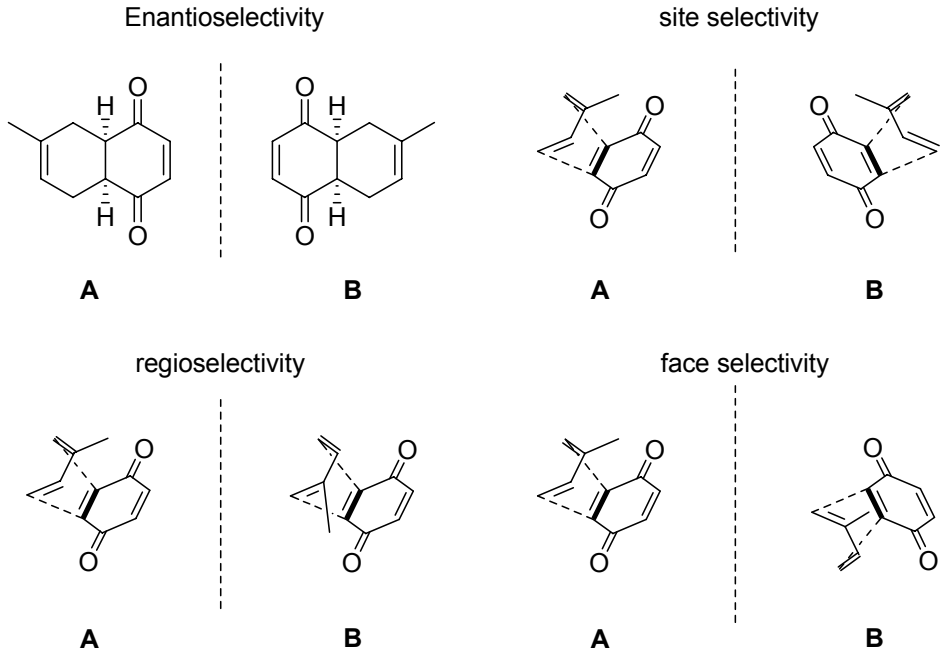
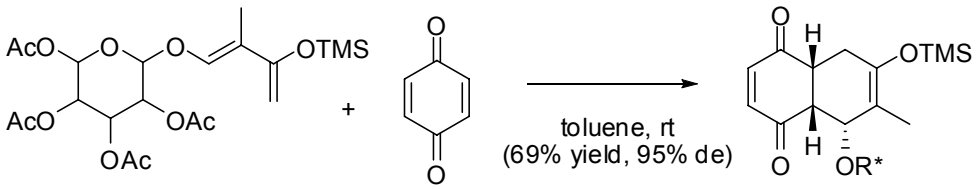


Figure 8. Control elements in enantioselective quinone Diels-Alder reaction

The enantioselective quinone Diels-Alder reaction is challenging because of the multiple requirements of high face-selectivity, regio-selectivity (i.e., only one of the two possible modes of coupling an unsymmetrical diene and

a unsymmetrical dienophile), and site-selectivity (i.e., reaction at only one of the C=C subunits of an unsymmetrical quinone). Several approaches to this problem have been reported.

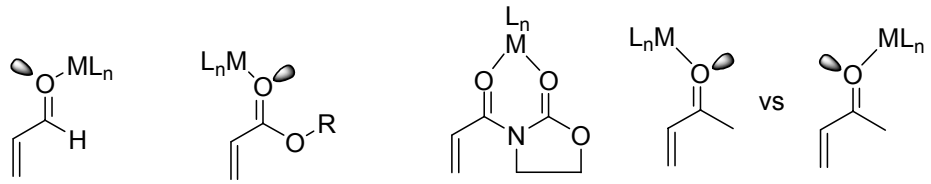
2.2.2 Use of a chiral diene



263 **264** **265**

Between 1983 and 1989, Stoodley[121-123] et al. reported the preparation of several chiral alkoxy dienes based on a peracetylated glucopyranosyl auxiliary. Although good diastereoselectivity was observed with the highly reactive benzoquinone, the authors did not extend the scope of the method to any other quinone, which has proven to be less reactive.

2.2.3 Chiral Lewis acid catalyzed reactions



steric control stereoelectronic chelation control lone pair symmetry

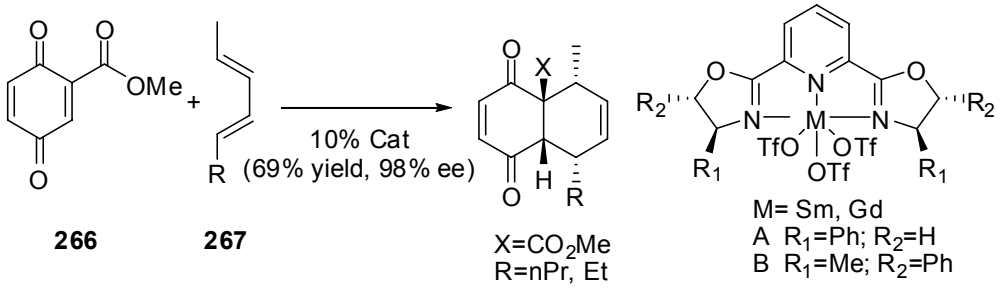
Figure 9. Lewis acid coordination with α, β-unsaturated carbonyls

The success of chiral Lewis acid-mediated Diels-Alder reactions relies on the selectivity of the coordination of the carbonyl with the Lewis acid (for

dienophiles containing α, β–unsaturated carbonyls) and a highly organized transition state. Selective coordination usually depends on steric control (aldehydes), stereoelectronic control (esters, amides), or chelation control. Lewis acid coordination is usually a nonselective process with unsaturated ketone dienophiles because the participating lone pairs are positioned in similar steric and electronic environments (**Figure 9**).

2.2.3.1 Evan's catalyst

In most cases, formation of a highly organized transition state relies on two-point ligation of a chiral catalyst to the dienophile, often a dicarbonyl system[124], so that only one face of the dienophile is exposed to the diene partner. Single-point ligation often leads to poor levels of enantiocontrol and, ultimately, has limited the use of simple ketone dienophiles, such as quinones, in catalytic asymmetric Diels-Alder reactions. Single-point ligation of an achiral dienophile to an asymmetric catalyst generally requires a secondary interaction, either electronic or steric, between the dienophile and catalyst for good enantioselectivity.

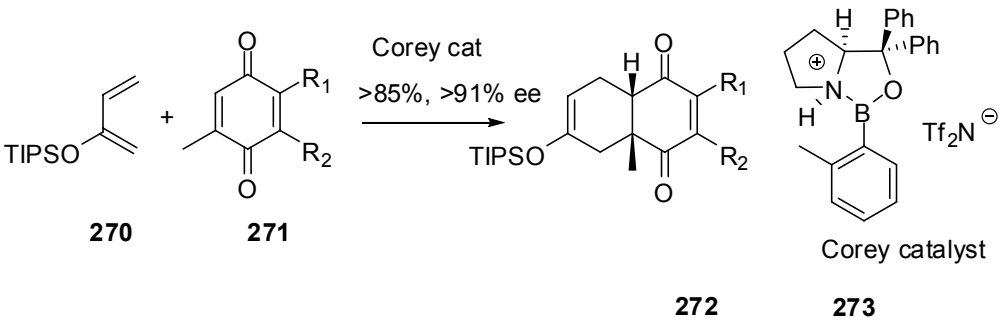


266 **267** **268** **269**

One recent example reported by Evans *et al.* involves a DA reaction of substituted benzoquinone **266** catalyzed by chiral rare earth Lewis acid **269**. The ester group present in the benzoquinone **266** activates the attached double bond and provides an extra binding site that directs Lewis acid coordination to the adjacent carbonyl group of the quinone. The diene selectively adds to the more hindered double bond with high regio and enantioselectivity indicating the transition state is well controlled by the

multiligation strategy.

2.2.3.2 Corey's catalyst



270 **271** **272** **273**

The chiral cationic oxazaborolidinium ion **273** developed by Corey *et al.* is a useful and potent catalyst for promoting a wide variety of highly enantioselective Diels-Alder reactions.[125] The catalyst has been applied to a number of enantioselective reactions of unsymmetrical 1,3-dienes with quinones.[126] These results provide guidance for the general use of the catalyst in quinone Diels-Alder reactions, which are summarized below.

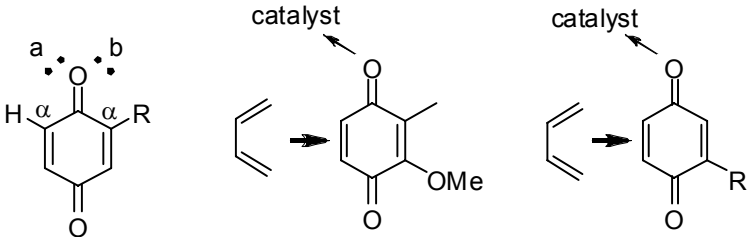


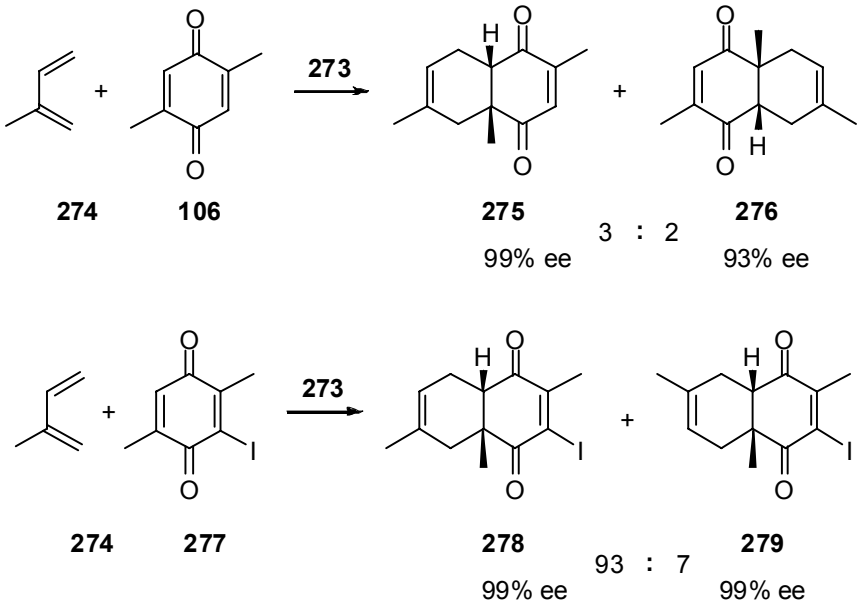
Figure 10. Lewis acid coordinate to quinone carbonyl group.

(1) For a quinone carbonyl flanked by a C-H and a C-R, the major product will result from catalyst coordination preferentially at the oxygen lone pair on the C-H side (a) rather than the C-R side (b) because (a) is sterically more accessible than (b); (2) Catalyst coordination at the more basic of the two 1,4-quinone oxygens will predominate and will lead to the preferred

Diels-Alder adduct; (3) A quinone C=C bond with two hydrogens is more reactive than one bearing a substitutent, especially a σ-electron donating group; (4) For monosubstituted 1,4-quinones (or p-benzoquinone itself), the major product pathway will involve coordination of the catalyst at the C=O syn to the HC=CH subunit that undergoes [4 + 2]-cycloaddition; (5) C(1) of 2-triisopropylsilyloxy-1,3-butadiene (**270**), the more nucleophilic end of the diene, will bond to the carbon distal from the carbonyl group that coordinates to the catalyst, i.e., the more electrophilic carbon.

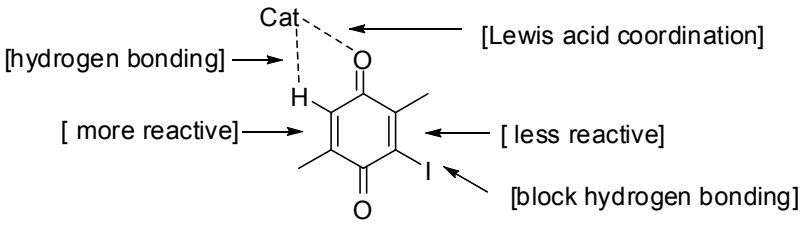
The use of 2,5-dimethyl-1,4-benzoquinone as a dienophile was of special interest because the expected coordination of the catalyst to the carbonyl lone pair anti to methyl would activate both C=C subunits of the quinone, leading to both possible adducts, as shown in **Scheme 48**.

Scheme 48



Corey's solution to this problem involved the utilization of 3-iodo-2,5-dimethyl-1,4-benzoquinone as a synthetic equivalent of 2,5-dimethyl-1,4-benzoquinone. The iodide substituent in the quinone deactivates the C=C subunit to which it is attached (C=C protection) and

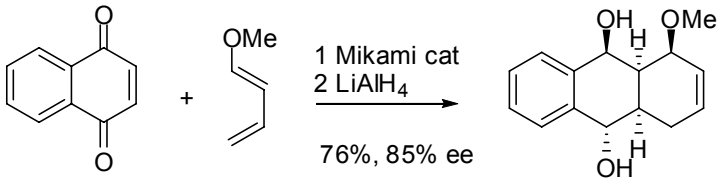
also blocks catalyst coordination to the carbonyl lone pair which is syn to the iodine. In consequence, there is only one carbonyl lone pair in 3-iodo-2,5-dimethyl-1,4-benzoquinone that is sterically accessible for coordination with catalyst.



277

Figure 11. Control element in 3-iodo-2,5-dimethyl-1,4-benzoquinone

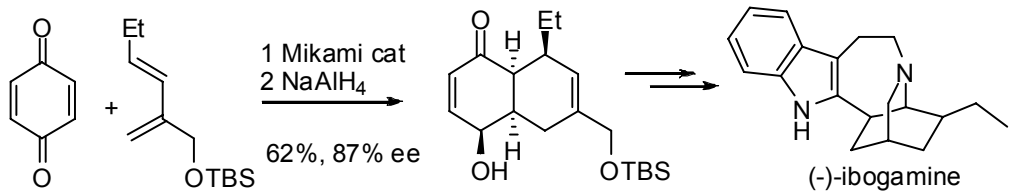
2.2.3.3 Mikami's catalyst



280 **281** **282**

Mikami[127] *et al.* developed a chiral titanium catalyst that successfully catalyzed an enantioselective Diels Alder reaction of **281** with naphthoquinone **280**. The catalyst used was derived from the reaction of (R)-BINOL with $Cl_2Ti(Oi\text{-}Pr)_2$ in the presence of 4 Å molecular sieves and H_2O (referred to herein as the Mikami catalyst).[45,128] Wright successfully used this catalyst in a total synthesis of ibogamine, which was the first asymmetric total synthesis relying on an enantioselective quinone Diels Alder reaction (**Scheme 49**).[129]

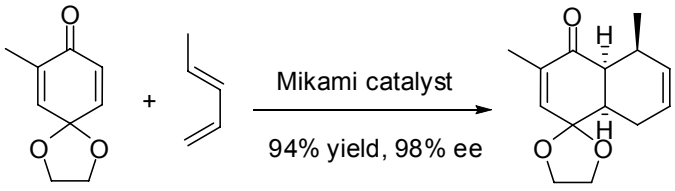
Scheme 49



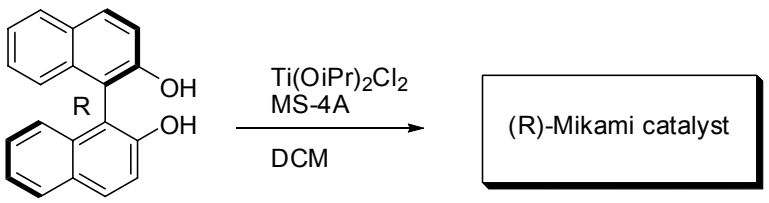
264 **283** **284** **285**

It has been suggested that quinone ketals might be more useful quinone surrogates in these reactions (**Scheme 50**).[130] There are a number of potential advantages of 1,4-quinone monoketals over the corresponding quinones, including: (1) monoketals are expected to be more Lewis basic; (2) they would provide adducts that do not undergo facile aromatization; (3) monoketals provide adducts in which one of the two carbonyls of the 1,4-quinone is already protected, simplifying the task of further selective transformations.

Scheme 50



286 **274** **287**



288

The Mikami catalyst has been applied to enantioselective carbonyl addition,

ene reaction, aldol reaction, Michael reaction, [2+2] and [2+3] cycloadditions and Diels-Alder reactions. Despite the importance of these titanium BINOL complexes in asymmetric syntheses, there is very little information regarding the actual structure of this catalyst. A recent study on (BINOLate)Ti(O^iPr)$_2$ catalyst suggests three different BINOLate titanium complexes, and all of them are potential catalysts or pre-catalysts (**Figure 12**). This study suggests that the actual structure of the Mikami catalyst might be difficult to determine due to the aggregation of titanium species.

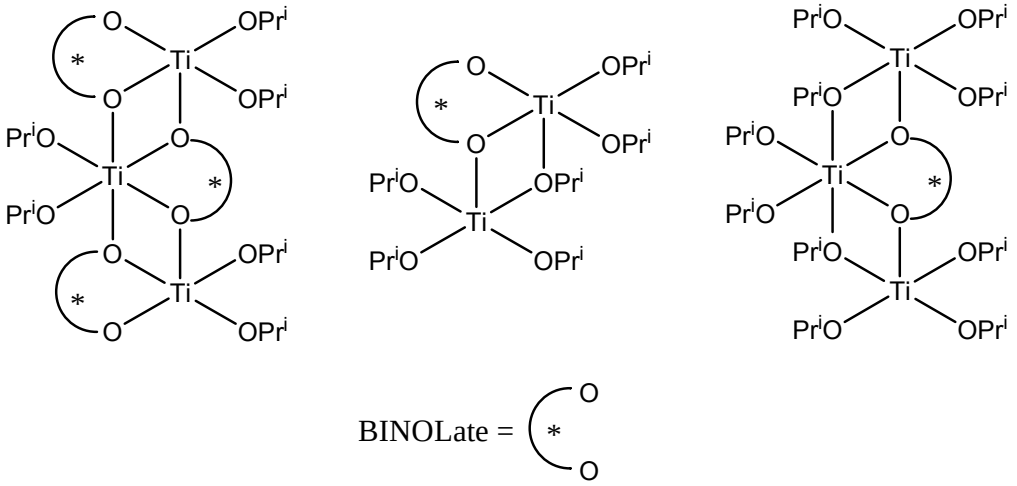
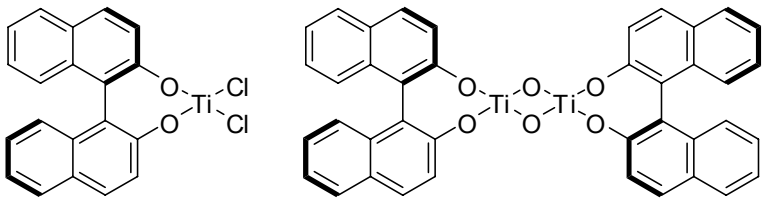


Figure 12. Some proposed structures for titanium/BINOL catalyst based on X-ray analysis

In the early study, the structure of the active titanium catalyst was assumed to be the BINOL-derived titanium dichloride **289**.[45]

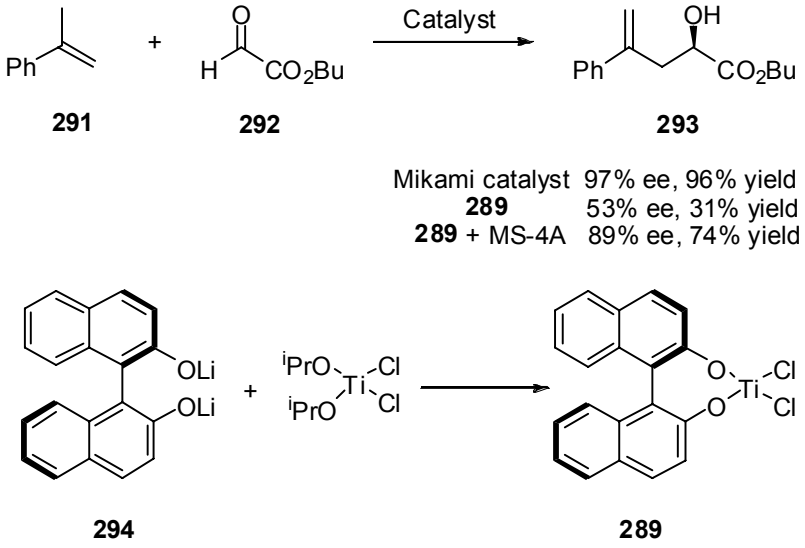


289 **290**

Figure 13. Two proposed structures for Mikami's catalyst

However, the dichlorotitanium complex **289** prepared from $TiCl_4$ and BINOL dilithium salt does not show the same reactivity as Mikami catalyst (**Scheme 51**). In the glyoxylate–ene reaction, the dichlorotitanium complex **289** gives the ene product **293** in low yield along with a low % ee. By contrast, use of **289** treated with commercially available MS-4A significantly increases the chemical yield and gives a higher % ee. This experiment suggests that the MS-4A converts the pre-catalyst **289** into the active BINOL-Ti catalyst.

Scheme 51



An analytical sample of the Mikami catalyst was prepared from BINOL and $[TiCl_2(O^iPr)_2]$ in the presence of MS 4A doped with $H_2{}^{17}O$. The ^{17}O NMR spectrum of the active BINOL–Ti catalyst in toluene-d_8 reveals peaks only in the μ3-oxo (Ti_3O) region (δ 520–590). Furthermore, elemental analysis of the active catalyst revealed only a low amount of Cl (Found: Ti, 11.4; Cl, 0.6%; Cl/Ti = 0.07. Calc. for **289**: Ti, 11.9; Cl; 17.6%). These results suggest that the active species of the chiral titanium catalyst is not the dichlorotitanium complex **289** but a μ3-oxo (Ti_3O) **290** (**Figure 13**).

Mikami observed a remarkable non-linear effect with this catalyst. For example, in a standard glyoxylate-ene reaction, the use of a catalyst

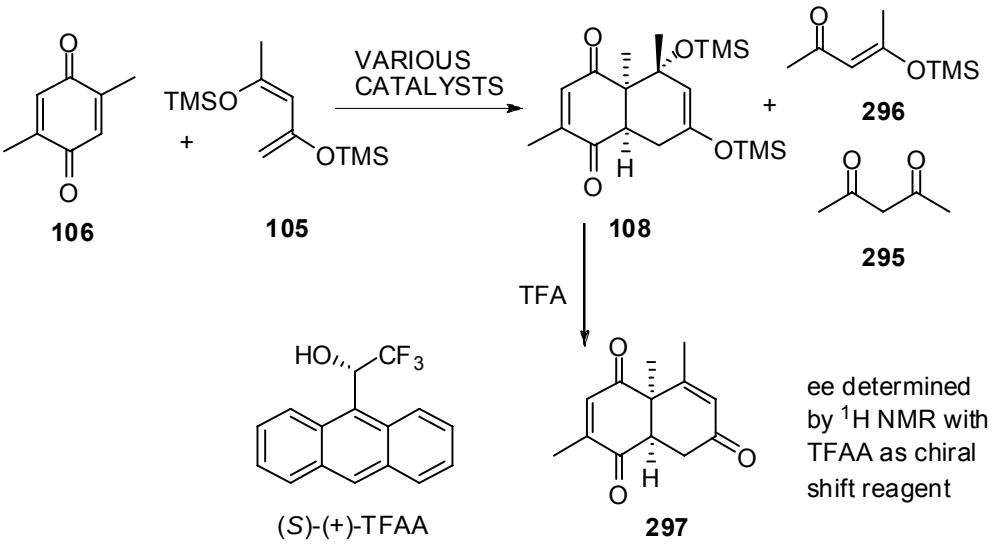
prepared from BINOL of 33% ee provided the ene product with 91% ee in 92% chemical yield. The ee thus obtained is not only much higher than that of the BINOL employed, but also very close to the value (94.6% ee) obtained by use of enantiomerically pure BINOL. This result implies that the active catalyst is a dimer (or oligomer) and that homochiral aggregates are more reactive than heterochiral aggregates.

2.2.4 Development of an enantioselective Diels-Alder reaction of 105 with 106

2.2.4.1 Preliminary attempts

Initial attempts to effect an enantioselective Diels-Alder reaction of 2,5-dimethylbenzoquinone (**106**) with diene (**105**) using the Mikami catalyst failed (**Scheme 52**). The reaction according to White's general protocol[131] gave cycloadducts in no more than 5% yield. This result was attributed to the low reactivity of **106** and the instability of **105**.

Scheme 52



It should be noted that the reaction of benzoquinone with diene **105** was complete within a minute at room temperature while the reaction with 2,5

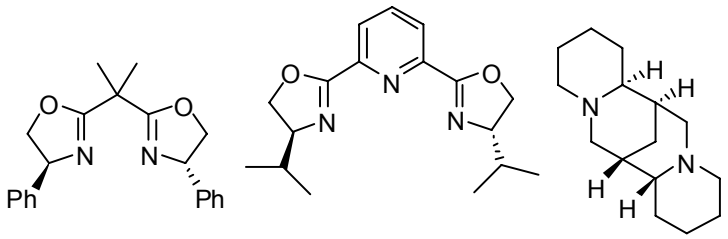
dimethylbenzoquinone required 48 h at 140°C to reach completion. In addition, diene **105** is readily hydrolysed and much less stable than the simple diene **283** used by White (**Scheme 49**). Increasing the amount of catalyst simply destroys the diene **105**.

2.2.4.2 Other Lewis acid catalysts

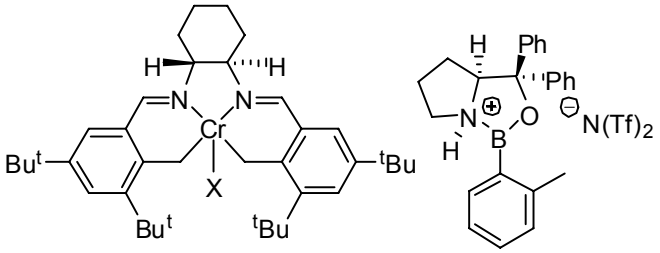
Enantioselective Diels-Alder reactions of **105** with **106** catalyzed by Lewis acids other than Mikami's catalyst were also investigated (**Scheme 52, Table 1**). Initially, achiral Lewis acids were tested for catalytic activity and diene stability. Among the various Lewis acids tested [$Ti(O^iPr)_4$, $TiCl_2(O^iPr)_2$, $(Chx)_2BCl$, $B(O^iPr)_3$, $ZnCl_2$, Me_3Al, $MgBr_2$], only magnesium bromide was efficacious. Although substantial diene decomposition occurred in the presence of $MgBr_2$, the addition of Et_3N gave a 50% yield of the desired aduct **108**.

Table 1: Yield and ee of **108** obtained from Diels-Alder Reaction of **105** and **106** using chiral Lewis acids

Run	*Catalyst*	*Yield %*	*ee %*
1	MeMgBr / **298**	47	15
2	MeMgBr / **299**	17	< 5
3	$MgBr_2$ / **300**	50	< 5
4	**301** (X=Cl)	40	33
5	**301** (X=SbF_6)	20	66
6	$AlMe_3$ / BINOL (**288**)	90	50
7	**302**	0	---



298 **299** **300**



301 **302**

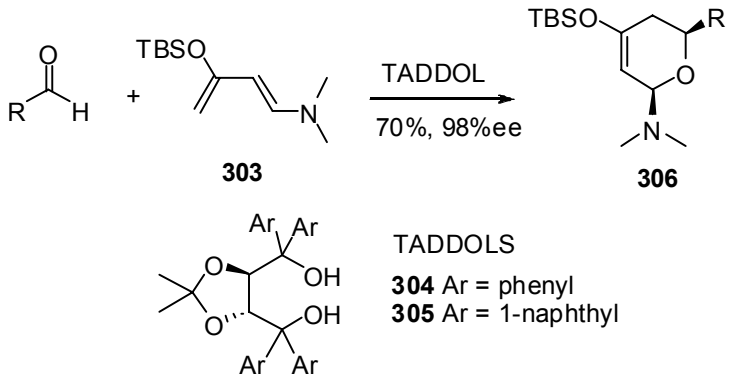
Based on the above results, three well known chiral magnesium bromide catalysts were tried; however, the enantioselectivities of these reactions were moderate (**Table 1**). Some additional chiral Lewis acids were also screened. Diene **106** decomposed in the presence of Corey's catalyst (**302**) under the reported conditions. Jacobsen's chromium salen catalyst (**301**) has been successfully applied in hetero-Diels-Alder reaction with Rawal's amino-diene, which is also an acid sensitive diene.[132-137] However, the chloride version of this catalyst gave poor enantioselectivity in the reaction of **105** with **106**. The selectivity was improved using the catalyst with a less coordinating SbF_6^- counter ion. Aluminum BINOLate catalysts have been successfully employed in a variety of Diels-Alder reactions.[138,139] Although the catalyst prepared from 1:1 mixture of Me_3Al and BINOL effectively promoted Diels-Alder reaction of **105** with **106**, the enantioselectivety was modest.

2.2.4.3 Organocatalysis

The enantioselective catalysis of organic reactions using small organic molecules as catalysts is a rapidly growing research area. In principle, the proton can be considered the smallest hard Lewis acid to activate the

carbonyl group of a dienophile and catalyze the Diels-Alder reaction. Very recently, Rawal has reported that some chiral alcohols are able to catalyze the Diels-Alder reaction of aldehydes with the amino-diene **303** (**Scheme 53**).[140] However, applying this approach to the reaction of **105** and **106** was not very successful (**Scheme 52**). No product was observed from the reactions catalyzed by TADDOL catalysts **304** or **305**. The reaction mediated by BINOL gave a 50% yield of the desired adduct **108** after 4 days at room temperature; however the ee was only 5%.

Scheme 53

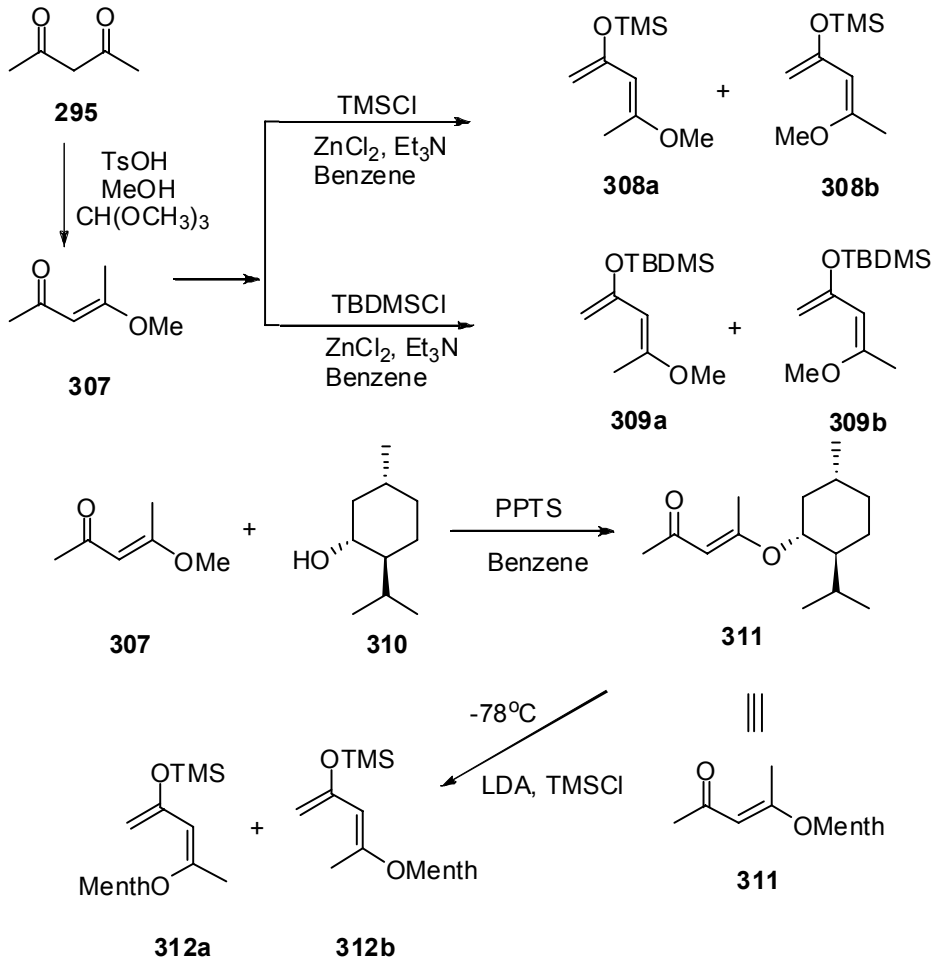


2.2.4.4 Stabilizing the diene **105**

The previous results suggested that the stability of diene **105** was problematic in attempted Lewis acid mediated Diels-Alder reactions with **106**. Optimization was therefore focused on modifying the reaction conditions to improve the stability of diene **105**. The first assumption was that the HCl generated during the titanium catalyst formation was detrimental to the diene. Control experiments indicated that **105** was more stable to $TiCl_2(O^iPr)_2$ in the presence of a hindered amine base (e.g. 1,2,2,6,6-pentamethyl piperidine). However, no Diels-Alder adducts with **106** could be obtained under these conditions, presumably because the added base deactivated the Ti(IV) Lewis acid. The methoxy dienes **308-309**

were prepared in hope that they would be more stable to hydrolysis than **105** (Scheme **53**). However, these dienes were also hydrolyzed by Mikami's catalyst and the Diels-Alder adducts with **106** were not obtained.

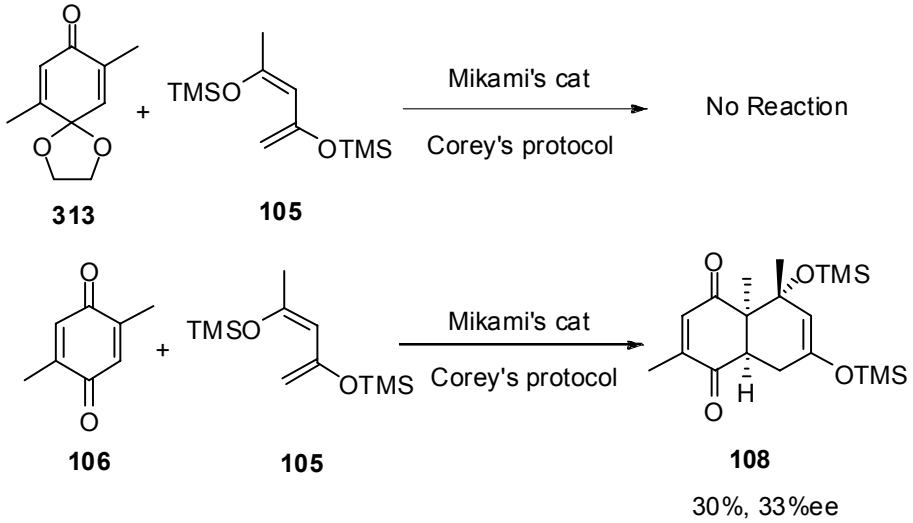
Scheme 54



Similar chiral dienes **312** were also prepared. These dienes were very unreactive. For example, reaction with **106** did not give Diels-Alder adducts after 48h at 140°C.

2.2.4.5 Systematic Investigation with the Mikami Catalyst

Scheme 55



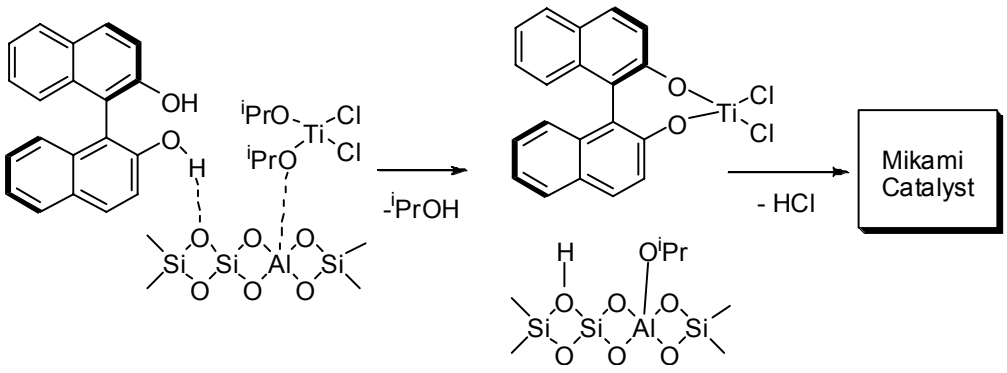
In 2003, Corey reported a catalytic enantioselective Diels-Alder reactions of 1,4-quinone monoketals using Mikami's catalyst.[130] In that paper, a different protocol to prepare the titanium BINOLate complex was described. Although using this catalyst failed to give the Diels-Alder adduct from **313** and **105**, a similar reaction of **105** with **106** gave **108** in 33% ee and 30% yield (**Scheme 55**). This result indicates that the procedure of making the catalyst is crucial. Therefore, the following conditions were systematically investigated:

- amount of MS-4A;
- moisture content of MS-4A;
- amount of the catalyst;
- ratio of $TiCl_2(O^iPr)_2$ and BINOL;
- additives

The Effect of Molecular Sieves (MS-4A)

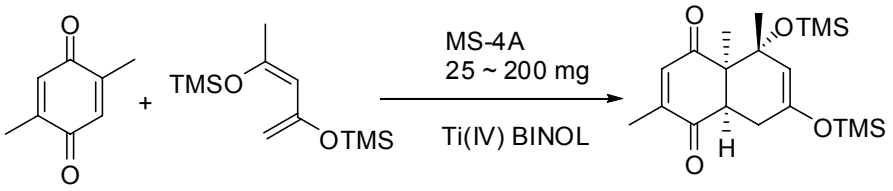
The structure of the Mikami catalyst is unknown, but it appears to involve μ-oxo bridges between at least two titanium centers. To convert the pre-catalyst into this active form, the MS-4A not only serves as the H_2O donor to hydrolyze the titanium chloride pre-catalyst but also as a base to trap HCl. This mechanism suggests that the amount of the molecular sieves and the moisture content of the molecular sieves will affect the catalyst structure and reactivity.

Scheme 56



As illustrated in Table 2, DA reactions of **105** with **106** catalyzed by Mikami's catalyst were indeed affected by the amount of MS-4A. The yield of the reaction increased when more MS-4A was used (c.f. entries 2-3). However, the reaction failed with larger amounts of MS-4A (entry 4). The best range seems to be 50~100 mg per 10 μmol of the titanium complex. One hypothesis is that MS-4A removes any acidic species, which are detrimental to the diene, thereby improving the yield of the reaction. At the same time, the titanium-BINOL catalyst is also absorbed by the MS-4A, the large excess of MS-4A results in insufficient catalyst to promote the reaction.

Table 2: The effect of the amount of MS-4A used in preparation of the Ti(IV) BINOL catalyst on the DA reaction of **105** and **106**



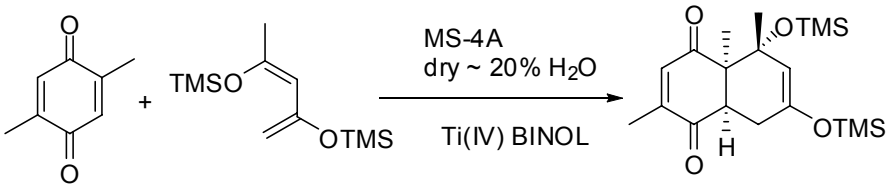
106 **105** **108**

run	MS-4A[a]	Time	Yield[b]	ee%[c]
1	25 mg/μmol [d]	2 d	18	67
2	50 mg/μmol	2 d	21	67
3	100 mg/μmol	6 d	52	43
4	200 mg/μmol	6 d	0	---

a. Contains 15% H_2O by mass; b. μmol of Ti, catalyst prepared by Corey's protocol;[130] c. Based on NMR of the crude reaction mixture; d. Measured by NMR with TFAA as the chiral shift reagent.

The H_2O contained in the sieves is important in giving the active BINOL–Ti catalyst.[128,141,142] MS-4A can be dried by heating at 180°C under vacuum. From gravimetric analysis, the H_2O content in the commercially available activated MS-4A employed in the catalyst preparation was found to be 5% w/w. By contrast, the H_2O content of old MS-4A (20 year) was found to be 20% w/w. It's worth noting that the "wet" MS-4A is much better than the "dry" one. The catalyst prepared from dry MS-4A can hardly promote the asymmetric Diels-Alder reaction of **105** and **106** (c.f. Table 3 entry 1).

Table 3: The effect of moisture on the preparation of the Ti(IV) BINOL catalyst for Diels-Alder reaction of **105** and **106**



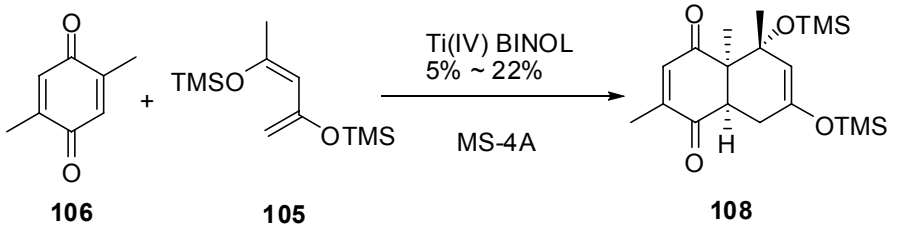
106 **105** **108**

run	*H_2O%w/w* [a]	*Method*	*Yield*[b]	*ee%*[c]
1	Dry	180°C /0.01mmHg	12	20
2	5%	dry/20% 3:1[d]	18	33
3	5%	dry+DCM/H_2O[e]	23	67
4	10%	dry+DCM/H_2O	33	78
5	15%	130°C 7d[f]	21	67
6	20%	180°C 2h	25	82

a. H_2O in MS-4A w/w; b. Based on NMR of crude reaction mixture; c. Measured by NMR with TFAA as chiral shift reagent; d. Dry MS-4A mixed with "old" MS-4A (20% H_2O) 3:1 ratio; e. Water introduced to dry MS-4A by adding wet DCM (a known amount of water added to distilled dry DCM); f. "old" MS-4A (20% H_2O) kept in an oven at 130°C for a week

In contrast, the Mikami catalyst prepared in the presence of commercially available and unactivated MS-4A gave the product in higher chemical yield and much higher enantioselectivity (c.f. entry; 2-6). These results support the mechanism that MS-4A serves as an H_2O donor to hydrolyze the titanium pre-catalyst.

Table 4: The effect of the catalyst [a] loading on the Diels-Alder reaction of **105** and **106**.



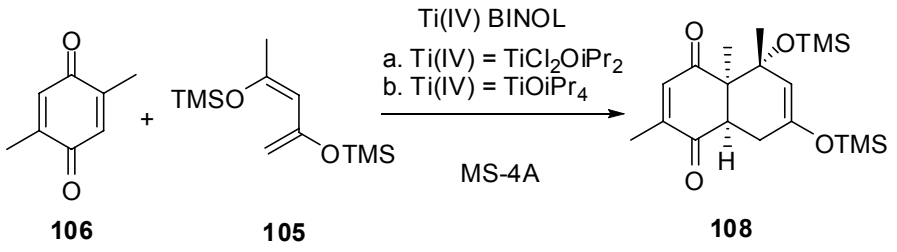
106 **105** **108**

run	*mol% of catalyst*	*%Conversion*	*[b]Yield%*	*ee%*
1	5	33	21	67
2	14	54	42	87
3	22	23	18	89

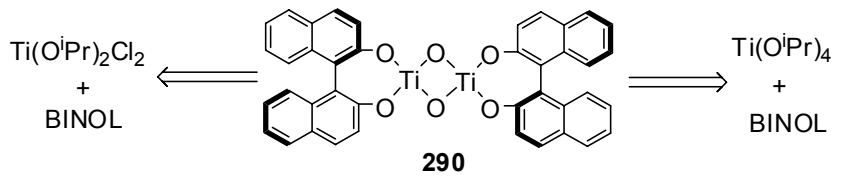
a. Catalyst prepared with 50mg MS-4A (15% H_2O) per 10μmol Ti(IV); reaction in DCM at room temperature for 72h; b. measured by NMR of the crude reaction mixture.

The catalyst loading of the DA reaction of **105** and **106** is limited by the stability of the acid labile diene **105**. Control experiments using impure (partially hydrolyzed) diene failed to produce DA adduct (<1%). This is attributed to a higher affinity of the hydrolized diene (i.e. **307**) for titanium catalyst than **106**. The data in Table 4 suggested that the maximum catalyst loading in the reaction was ca. 14 mol%.

Scheme 57



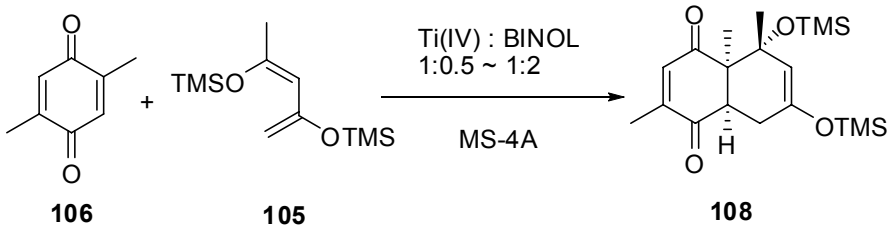
106 **105** **108**



290

Another approach to control the acidity of the catalyst is to change the titanium (IV) precursor. Mikami and Terada,[128] and later Nakai *et al.*, reported that reaction of (R)-BINOL with $Ti(O^iPr)_4$ and water, followed by heating and the azeotropic removal of isopropyl alcohol in refluxing toluene led to the formation of the same μ-oxo titanium complex **290**. The side product HCl can be avoided in this process. The stability of diene **105** in the reaction catalyzed by this catalyst (prepared from $Ti(O^iPr)_4$) was much improved. However, the reaction was much slower compared to the one using catalyst prepared from $TiCl_2(O^iPr)_2$ (20% yield, 25%ee, 2 day). This result suggests that **290** might not be the structure of the active titanium species.

Table 5: The effect of the Ti : BINOL ratio on the catalyst performance

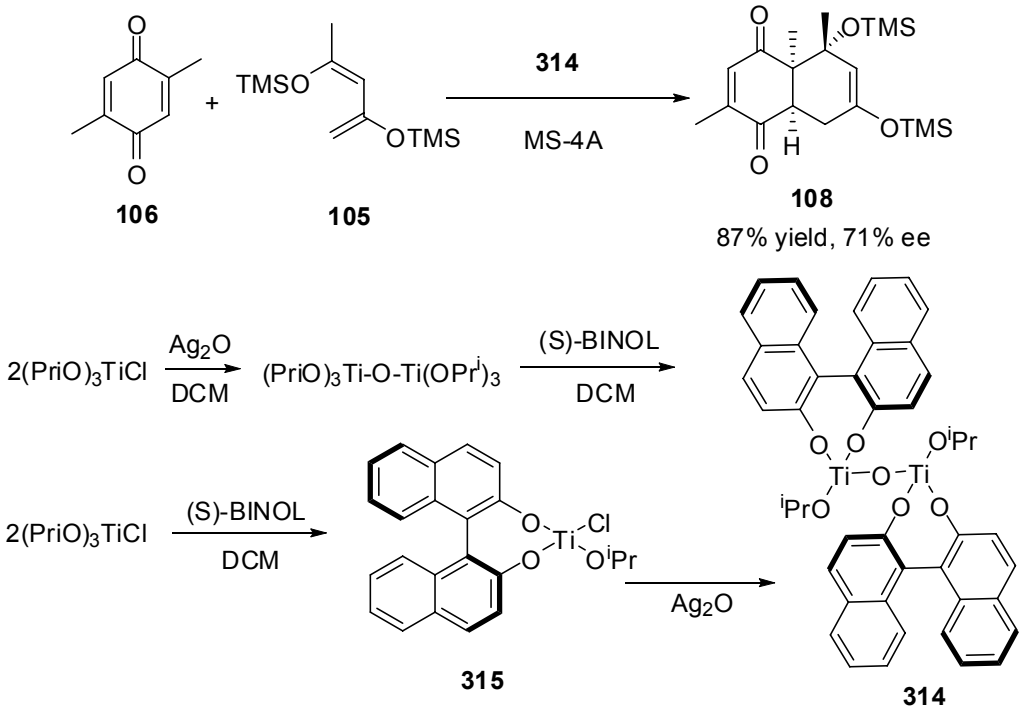


106 **105** **108**

run	*Ti : BINOL*	*Yield%*	*ee%*
1	1:0.5	66	33
2	1:1	65	82
3	1:1.5	50	78
4	1:2	57	58

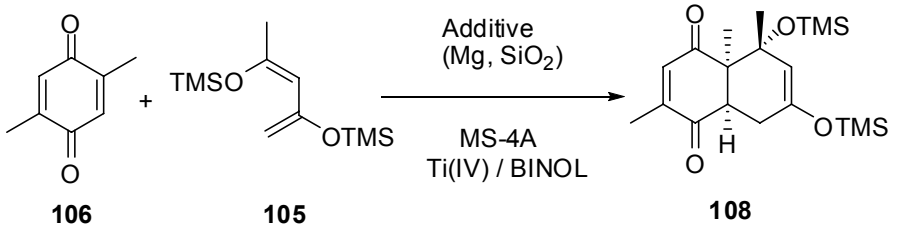
The proper ratio of titanium and BINOL is another key parameter for catalyst preparation. It was reported that catalysts prepared with BINOL to titanium ratios of 1:6, and 2:1 were optimal for asymmetric alkylation and asymmetric hetro-Diels-Alder reaction, respectively.[30] The results in Table 5 suggested that the catalyst prepared from a 1:1 ratio of BINOL to Ti (IV) was the optimal for the desired Diels-Alder reactions.

Scheme 58



Very recently, Maruoka[143] reported a new titanium catalyst **314** which can catalyze the asymmetric allylation of aldehydes. This catalyst can be generated by two different routes with Ag_2O as the additive. The proposed structure is a different form of μ-oxo titanium. Surprisingly, the Diels-Alder reaction of **105** and **106** catalyzed by **314** gave **108** in 87% yield and 71% ee after 2 days. Although the ee of **108** was lower than had been obtained with other catalyst preparations, the much improved conversion suggested that a better catalyst might be prepared with the right additive.

Table 6: The effect of additives on the Diels-Alder reaction of **105** with **106** using Mikami's catalyst.



106 **105** **108**

run	*Additive (amount)*	*Yield%*	*ee%*
1	----	21	67
2	Mg (5mg)	65	82
3	Mg (10mg)	69	79
4	Mg (20mg)	82	41
5	Silica (5mg)	72	75
6	Silica (5mg) Mg (5mg)	93	90

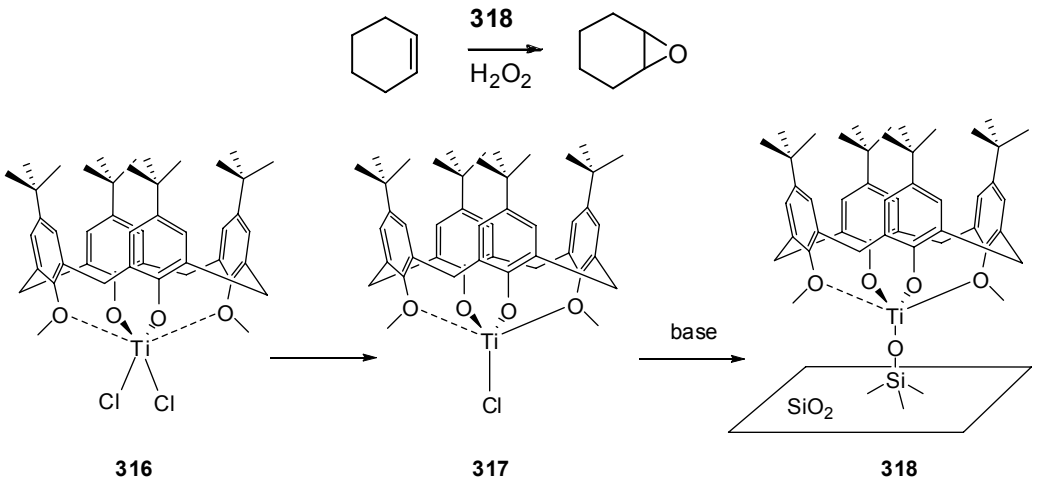
a. Reaction in DCM at room temperature for 48h using 5 mol% catalyst (relative to Ti). Catalyst prepared using Corey's protocol with MS-4A containing 5% water.

The effects of magnesium powder and silica powder as additives were considered for study (**Table 6**). Both are readily available and easily separated from the reaction mixture. The rationale for adding magnesium powder was to neutralize any trace amount of HCl and other acidic species and thereby stabilize the diene. Both the yield and enantioselectivity of the reaction increased dramatically with the proper amount of magnesium powder (c.f. Table 6 entries 1-4). It's important to note that the mass recovery of the intact diene also increased under these conditions, which provided a clue for further optimization.

The utilization of silica as an additive was based on the concept of "surface organometallic catalysts".[144] The surface organometallic catalyst consists of a transition-metal-containing active site that is grafted onto a solid support that serves as a rigid ligand for the metal center. It has been shown that the

immobilized form of the catalyst (i.e., **318**) was more than 20 times more active and far more selective than the solution-phase catalyst in olefin epoxidation reactions using organic hydroperoxides as oxidizing agents (**Shceme 59**).[145]

Scheme 59



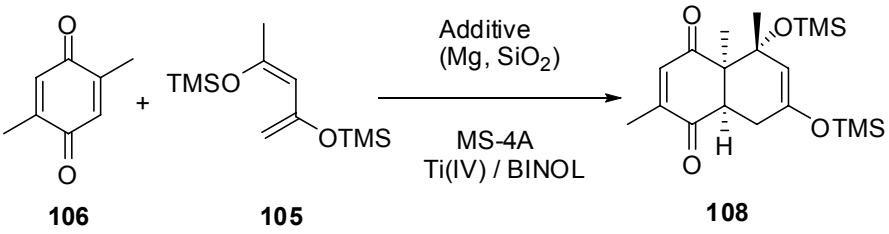
In the event, interesting and useful effects were observed including rate and selectivity enhancements, when silica was added to the titanium BINOLate catalyst (Table 6; c.f. entries 1, 2, 5, and 6). Optimal results were achieved with a combination of silica gel and magnesium powder (Table 6, entry 6).

2.2.4.7 Final optimization and scaling up of the D-A reaction

For practical synthesis, solvent-free conditions are ideal in terms of volumetric productivity and environmental safety. However, asymmetric catalytic processes are usually highly sensitive to solvents and the concentration of substrates. After careful optimization, much higher enantioselectivity (up to 95%) in the DA reaction of **105** with **106** was achieved under solvent-free conditions (**Table 7**). The optimized procedure involved adding **106** to a DCM solution of the Mikami catalyst prepared according to Corey's protocol using MS-4A containing 5-6% water (w/w).

After 1h, the diene **105**, Mg powder, and silica were added and the reaction mixture was concentrated to remove the DCM.

Table 7: The effect of concentration on the enantioselective (5% Mikami catalyst) Diels-Alder reaction of **105** and **106**.



106 **105** **108**

Run	*Concentration*	*Yield %*	*ee %*
1	0.28 M	93%	90%
2	neat	85 ~ 90%	> 95%

The workup and purification of a Diels-Alder reaction with a Danishefsky-type siloxydiene is challenging because of the instability of the adducts. Typically, the adducts are fully or partially hydrolyzed during workup or on silica gel using standard procedures. Distillation was very effective for purification of racemic **108** from thermal DA reaction of **105** with **106**. However, even trace amounts of titanium species in the crude product from the enantioselective DA reaction were detrimental and caused decomposition during attempted distillation. After numerous experiments, a workup protocol for large scale enantioselective DA reaction was developed that involved a non-aqueous workup followed by removal of the excess diene by fractional distillation under high vaccum. The quality of the product obtained from this was similar to that obtained by distillation in the thermal reaction and it could be used for the subsequent photo reaction directly.

2.2.4.8 Determination of the absolute configuration of **108**

In recent years there has been a marked increase in the number of papers describing the use of NMR for the assignment of the absolute

stereochemistry of organic compounds.[146] The general procedure consists of the derivatization of the substrate of unknown configuration with each of the two enantiomers of an auxiliary reagent. The proton NMR spectra of the resulting diastereoisomeric derivatives are compared and the differences in chemical shifts measured to give a $\Delta\delta^{SR}$ values. This method has been applied to secondary alcohols by preparing Mosher's ester (MTPA) derivatives.[147] The procedure for the assignment of the absolute configuration of a secondary alcohol bearing substituents L_1 and L_2 [i.e. $L_1L_2CH(OH)$], directly bonded to the stereogenic center, consists of a series of steps. These steps are as follows:

1. Esterification of the substrate with the R and the S enantiomers of Mosher's acid (MTPA). Assignment of the proton NMR signals from the L_1 and L_2 parts of both derivatives.
2. Comparison of the chemical shifts of the signals due to protons in L_1 and L_2 in both the R and the S derivatives and calculation of the corresponding differences expressed as $\Delta\delta^{SR}$. For each assignable proton, the $\Delta\delta^{RS}$ is defined as the chemical shift of the signal for that proton in the derivative prepared from the (*R*)-MTPA minus the chemical shift of the related proton in the derivative prepared from the (*S*)-MTPA ($\Delta\delta^{SR}L_1 = \Delta\delta^{S}L_1 - \Delta\delta^{R}L_1$). The signs of the calculated $\Delta\delta^{SR}$ (+ or -) should be the same for all of the protons from the L_1 substituent and opposite to those from the L_2 substituent.
3. Consider the model in Figure 14 and insert the substituent with a positive $\Delta\delta$ and that with a negative $\Delta\delta$ in the appropriate place. Assign the absolute configuration of the substrate accordingly (**Figure 14**).

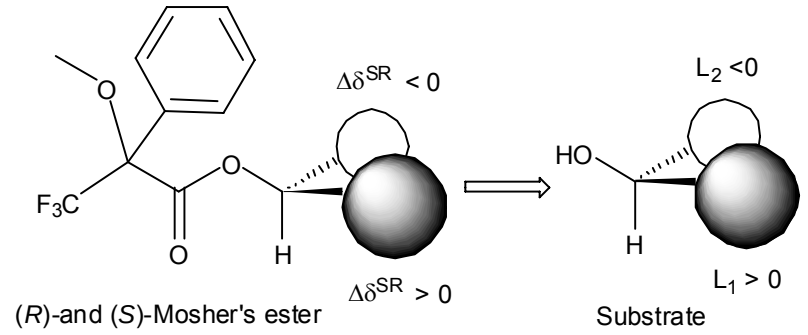
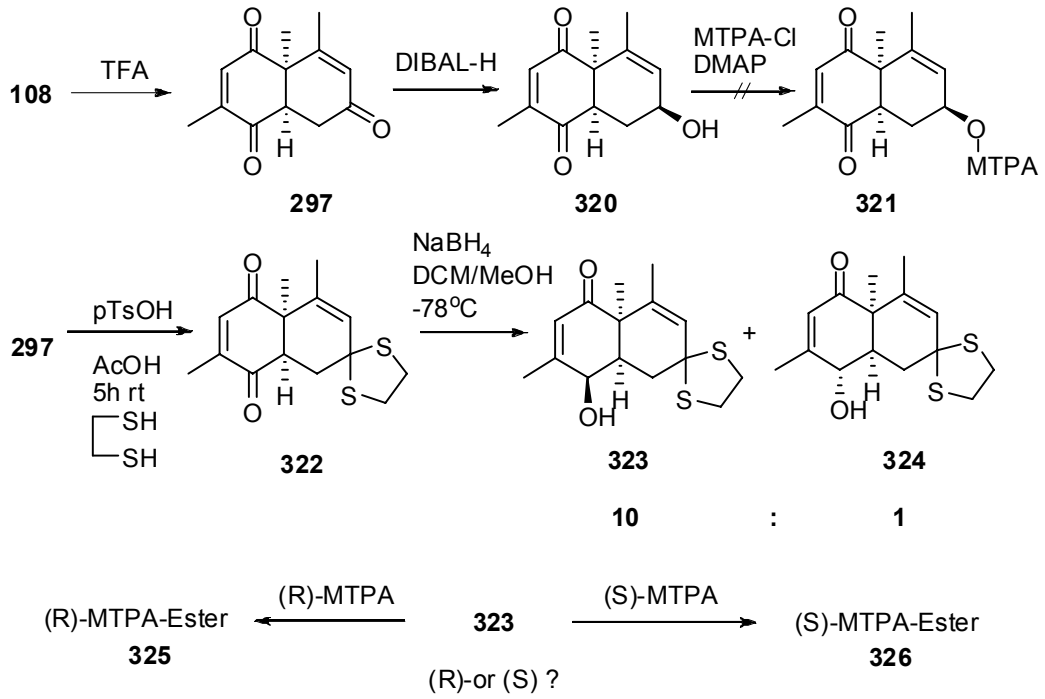


Figure 14. Model for assigning absolute configuration of **323** by NMR, from the signs of the calculated differences in chemical shift

Scheme 60



Hydrolysis of **108** with TFA gave the known[46,50] compound **297** (**Scheme 59**). Reduction of **297** with DIBAL-H selectively gave the alcohol **320**. However, attempts to prepare **321** from **320** were not successful. Alternatively, **297** was converted into **322** by treatment with ethanedithiol. Selective reduction[51] of **322** with $NaBH_4$ gave a separable 10:1 mixture of **323** and **324** respectively. The relative configuration of **323** was assigned

based on NOE experiments (**Figure 14**). Positive NOEs were observed at HC-8'a and H_3CC-4'a on irradiation of HC-8' and at HC-8'a, HC-8' and H_3CC-4 on irradiation of H_3CC-4'a. Esterification of **323** with (*R*)-MTPA and with (*S*)-MTPA gave **325** and **326**, respectively. The ^1H chemical shifts observed in the NMR spectra of **325** and **326** are shown in Table 7.

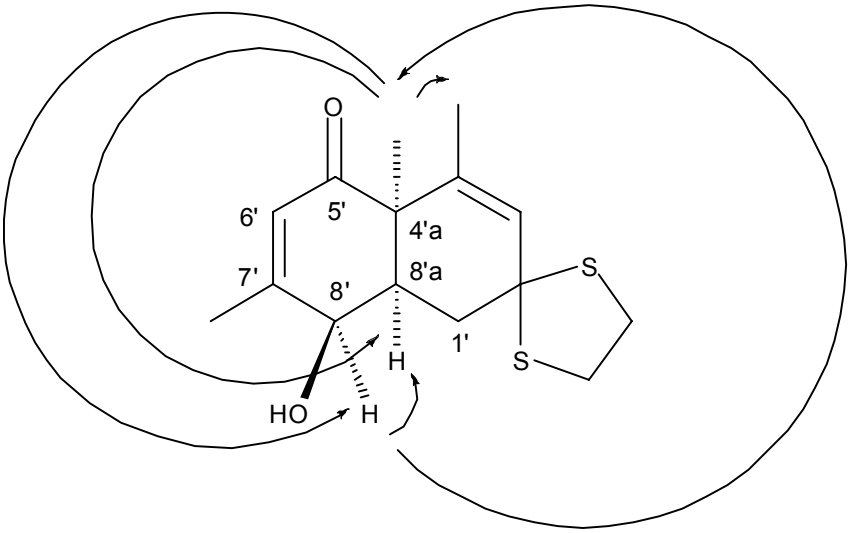
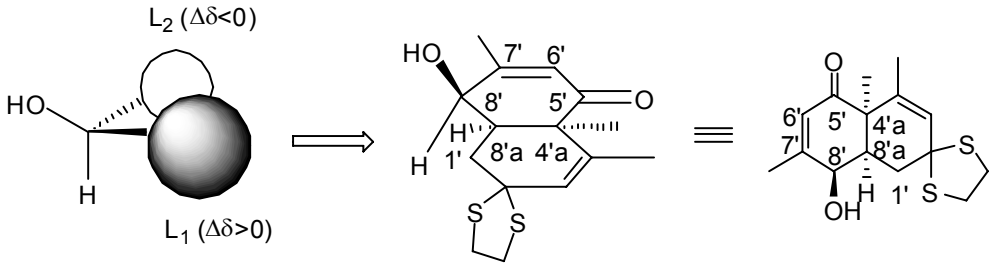


Figure 15. NOE correlations observed in **323**.

Table 8: ^{1}HNMR chemical shifts (in Hz at 500 MHz) for **325** and **326**.

	HC-6'	H_3CC-7'	HC-3'a	HC-1'α	HC-1'β	H_3CC-4'a	H_3CC-4'
326	2907.5	880.1	2860.6	1206.5	1030.3	709.7	1001.2
325	2915.7	931.9	2848.0	1128.9	995.2	708.3	995.2
$\delta_S - \delta_R$	-8.2	-51.8	+12.6	+77.6	+35.1	+1.4	+6.0
	$\Delta\delta^{SR} < 0$ (L_2)			$\Delta\delta^{SR} > 0$ (L_1)			



L_1 = HC-3'a, HC-1'α, HC-1'β, H_3CC-4'a, H_3CC-4'

L_2 = HC-6', H3CC-7'

Figure 16. Assignment of the absolute configuration of **323** by NMR.

The results in Table 7 clearly show that HC-6' and H_3CC-7' have negative value $\Delta\delta^{RS}$ and therefore belong to the L_2 substitute (see **Figure 16**). The remaining protons all show positive value $\Delta\delta^{SR}$ and belong to the L_1 substituent. Thus, the absolute configuration of **323** prepared from (*R*)-BINOL catalyzed Diels-Alder reaction of **105** and **106** is as illustrated. This result was confirmed by the X-ray analysis of **325** (**Figure 17**).

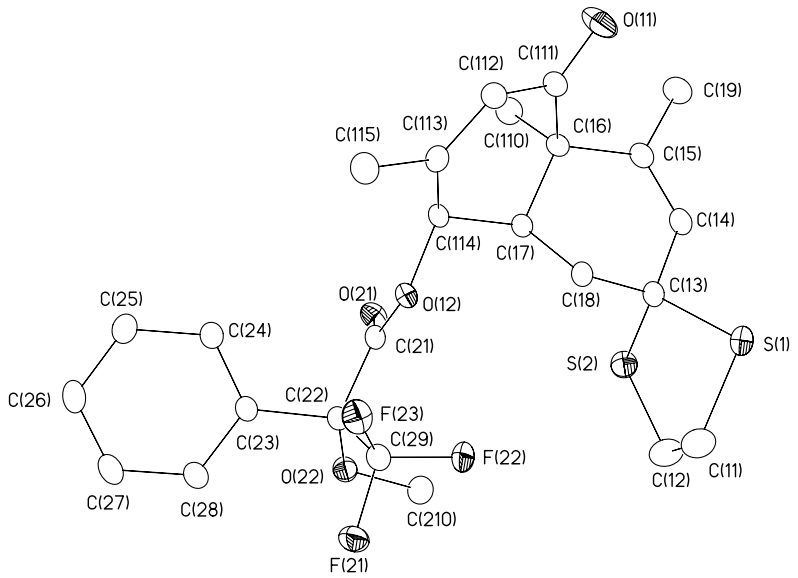


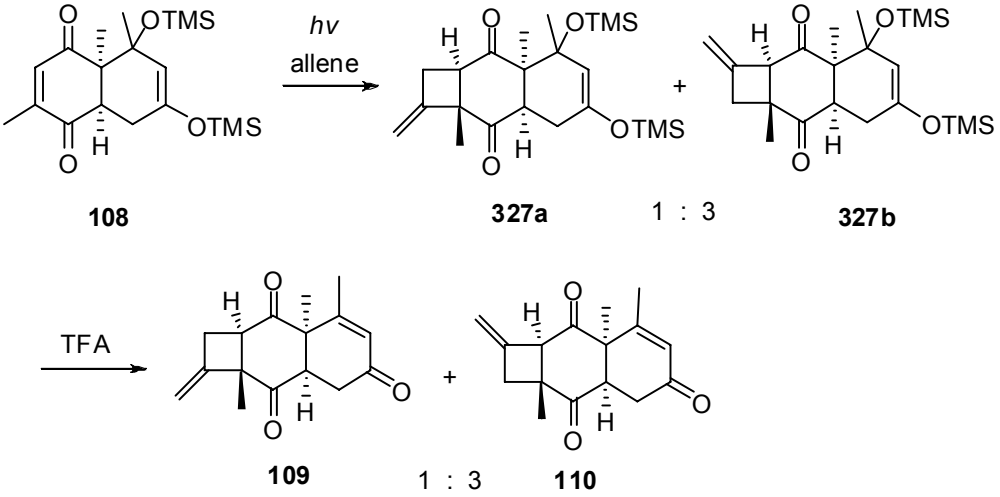
Figure 17. X-ray structure for **325**.

2.3 New route to the 5-6-6 tricyclic intermediate

2.3.1 Introduction

As in the racemic case,[50] the enaniomerically enriched Diels-Alder adduct **108** (>93%ee) underwent a photochemical [2 + 2] cycloaddition reaction with allene to give **327** as a 3 : 1 mixture of regioisomers, which was further hydrolyzed with TFA to give a 3:1 mixture of the known triketones[50] **110** and **109**, respectively.

Scheme 61



An objective of the second generation synthesis was to develop a more direct synthesis of **115** from **110** by reducing the number of functional group transformations used in the original route (see **Scheme 17**). To convert the hydrolyzed photoadduct **110** into **115** (**Scheme 62**), three issues must be addressed: i) cyclobutane ring has to be transform into the cyathin five membered A-ring; ii) stereoselective reduction of the carbonyl group on C-ring has to be developed; iii) epimerization of the B,C-ring junction from *cis* to *trans* (**Scheme 61**).

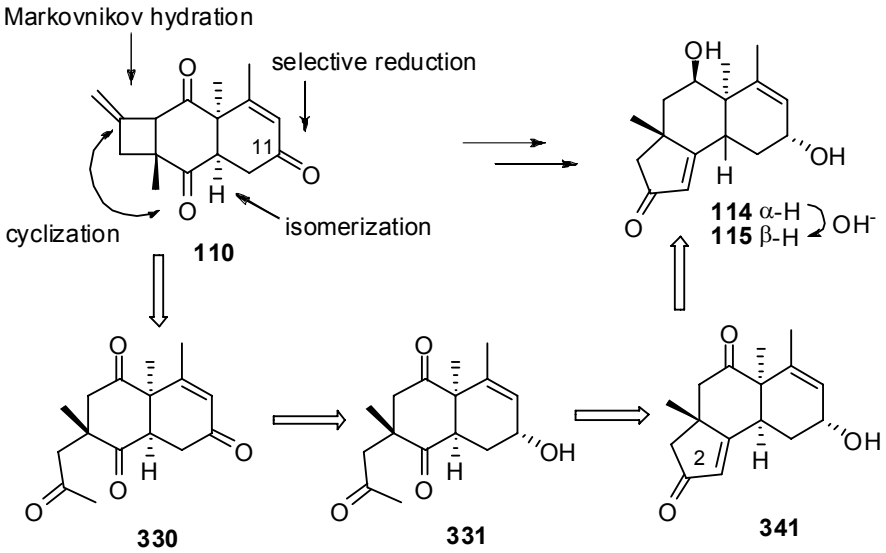
In the racemic route, the first issue was addressed by: i) chemoselective epoxidation; ii) addition of thiophenoxide to effect epoxide ring opening and retro-aldol; iii) aldol cyclization; iv) desulfurization (**Scheme 17**). It was

speculated that this overall transformation could be improved by using a more direct approach involving a Markovnikoff hydration of the exocyclic alkene. The resulting alcohol would then undergo a retro-aldol fragmentation of the cyclobutane moiety to give the methyl ketone **330**, that, in turn, could give the desired 5-membered ring (i.e., **341**) by the aldol-type cyclization. This overall transformation could be improved by using a more direct approach. This approach would shorten the previous route by two steps by avoiding the introduction and removal of the sulfide.

The second required transformation was previously achieved by: i) a chemo and stereoselective reduction of the enone carbonyl in **110**; ii) the eventual inversion of the configuration of the resulting alcohol by a Mitsunobu reaction; iii) hydrolysis of the Misunobu ester product (see **Scheme 17**). A more direct approach would involve reduction of the enone carbonyl with the desired stereoselectivity (e.g. **330**); shortening the route by two steps.

The isomerization of the 6,6-ring junction from *cis* to *trans* was efficiently achieved by treatment of **114** with NaOH as the equilibrium strongly favors **115** (see **Scheme 16**). By using the same strategy, compound **341** should be easily converted into **115**.

Scheme 62

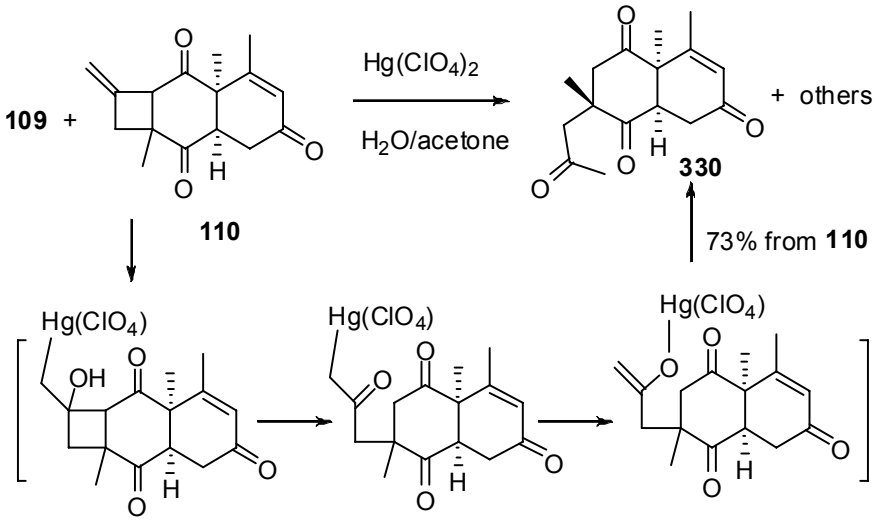


The presence of the enone in **110** was envisaged to facilitate the desired chemoselectivity. Thus, chemoselective reduction of the enone carbonyl should be possible because it is the least sterically hindered and is the most basic (i.e. more susceptible to an electrophilic reducing agent). Similarly, the exocyclic double bond in **110** is the most nucleophilic and should be more reactive than the enone towards acid-catalyzed hydration. Obbiously, the above reasoning dictates that olefin hydration should preceed carbonyl reduction.

2.3.2 Markovnikov hydration of the exocyclic olefin in 110

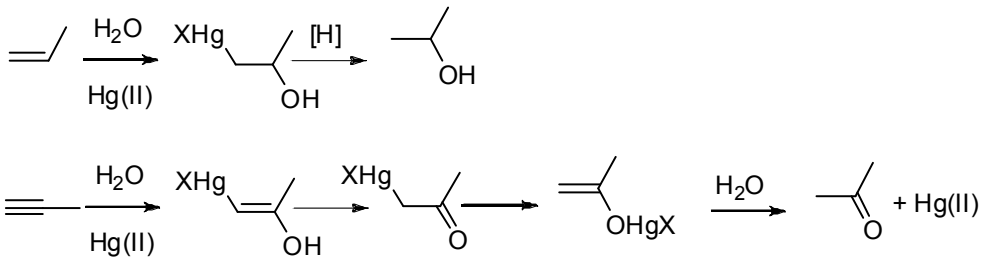
Initially, compound **110** was treated with $Hg(ClO_4)_2$ in wet acetone (5% H_2O v/v) to give **330** in moderate yield (<50%) (**Scheme 62**). Attempts to optimize the reaction by varying the amount of Hg (II) salt, the concentration, and reaction time were not succesful. In most cases, several unidentified side products were present along with the desired **330**. One hypothesis was that the nucleophilic addition of water to the intermediate mercurinium ion was a slow step allowing other pathways to compete (e.g. rearrangement). After considerable optimization, the Hg (II)-mediated hydrolytic ring opening step was achieved in excellent yield in 1:3 acetone:water.

Scheme 63



Typically, Hg(II)-mediated addition to alkene requires a stoichiometric amount of Hg(II) and a second reduction (or other) step to remove the Hg from the product (**Scheme 64**). It is noteworthy that the reaction of **110** to **330** is catalytic in Hg(II). This is easily rationalized by comparing the reaction to a Hg(II)-catalyzed hydration of alkynes. In contrast to alkene, Hg(II) mediated hydration of alkynes give α-mecurio ketones intemediates that lose Hg(II) by tautomerisation followed by hydrolysis (**Scheme 64**). Similarly, hydration of **110** produces α-mecurio ketone after retro-aldol of the initial oxy-mercuration product (**Scheme 63**).

Scheme 64



2.3.3 Stereoselective reduction of the enone carbonyl in 330

The chemo- and stereo-selective reduction of tetraone **330** is the key reaction of the 2nd generation route to **114**. To achieve chemoselective reduction of the enone carbonyl in **330** (the most basic) requires the use of an electrophilic reducing agent. Excellent chemoselectivity was obtained with 9-BBN as was observed previously[46] in the reduction of **328**. This reaction was expected to give the undesired alcohol **332**, as predicted by the concave 3D structure of **330** (and **328).** The reaction was attempted numerous times.

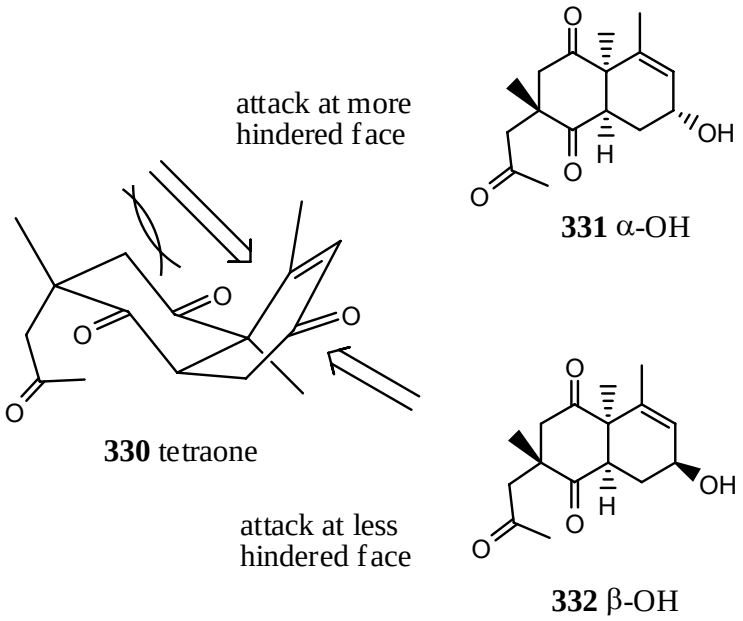
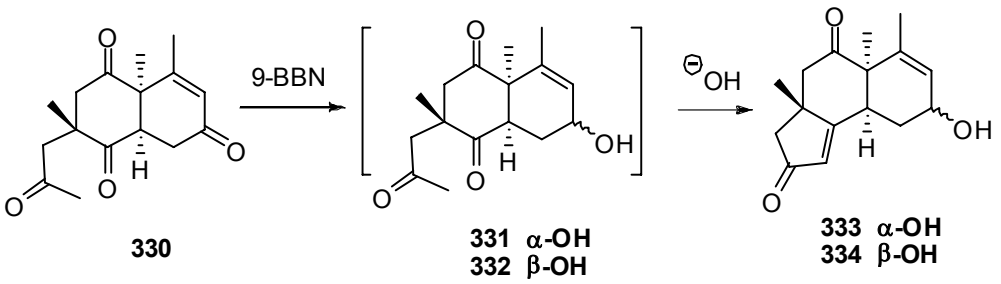


Figure 18. Model to explain the stereoselectivity of 9-BBN reduction of **330**.

Typically, reaction of **330** with 9-BBN followed by addition of KOH and heating under reflux produced the expected product **334** in low to modest yields. However, occasionally (but not reproducibly) the α-OH product **333** was obtained in variable yield (max. 45%) under seemingly the same conditions that usually gave **334**.

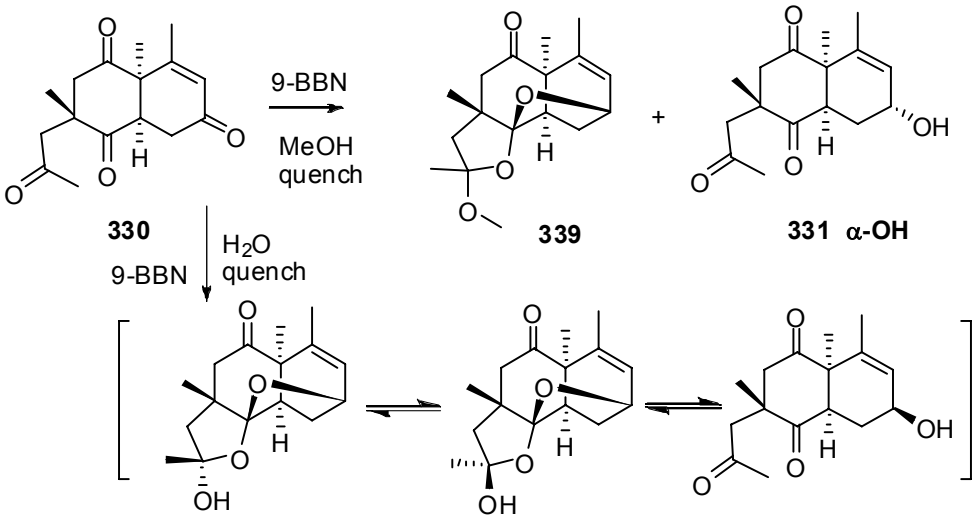
Scheme 65



Because the direct formation of **333** would be a significant improvement over the previous route, I set out to thoroughly investigate this 9-BBN reduction. Several initial attempts were not successful; the undesired **334** was the major product in all cases. The effect of concentration, temperature,

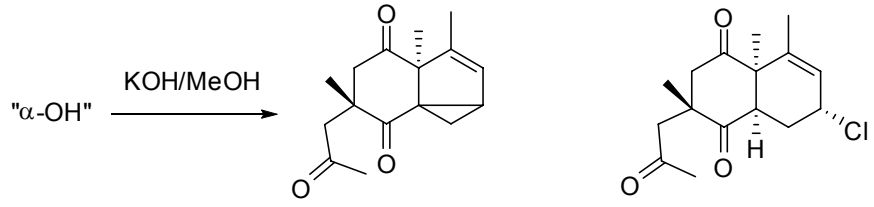
solvent, and the order of adding reagents were investigated without success. These results indicated that to facilitate understanding the origin of the occasional formation of **333**, all the important intermediates needed to be characterized (i.e. **331** and **332**). One hypothesis was that the α–OH product **331** was formed from **330** by a reaction that involved impurities in the commercial 9-BBN reagent. This might explain the irreproducible formation of **333** (the previously used bottle was exhausted and I was using a "new" bottle). To test this hypothesis, a better control of the quality of the 9-BBN was required. The commercial reagent (0.5 M in THF) was purified by precipitation and the precipitate was recrystalized from DME. The resulting needle crystals were used to prepare a stock solution of 9-BBN in THF. With this high quality 9-BBN reagent in hand, several reactions were attempted.

Scheme 66



The reaction of **330** with 9-BBN was quenched by addition of methanol followed by concentration and ^{1}H NMR analysis. Surprizingly, in almost all of the reactions, **339** was the major product with only a small amount of **332** being detected. The facile formation of **339** suggested that the hydroxyl group is perfectly positioned for addition to the carbonyl and even a weak

Lewis acid like methoxy-9BBN can catalyze the ketal formation. The β-alcohol **332** was the major product if the reaction of **330** with 9-BBN was quenched with H_2O. Little or no **331** was detected. It's worth noting that **332** is an equilibrium mixture of three components. Two of the three components involve intramolecular ketal formation consistent with the facile formation of **339**. Fractionation of the crude reaction mixture gave a low yield of **331** and **332** as well as **339**. The relative amount of **331** was not increased by controlled introduction of O_2 or protic species (H_2O, MeOH) to the 9-BBN reagent. Mass recovery was low regardless of the selectivity. One explanation for the poor mass balance was that the product was not free from the boron reagent. Another hypothesis was that **331** or **332** or both were further reduced under the reaction conditions. However, it was difficult to address these questions because of the complicated ^{1}H NMR spectrum of the crude product. An efficient protocol for analysis of the crude product was required.



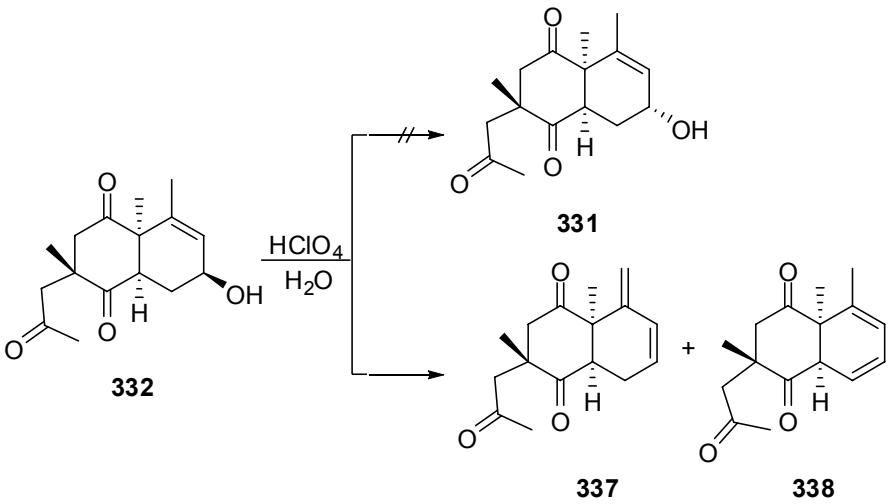
335 **336**

In the initial attempt, the crude product from 9-BBN reduction of **330** was treated with a stoichiometric amount of base, followed by neutralization with HCl. The reaction mixture was concentrated to dryness and analyzed by ^{1}H NMR. The amount of a new product, initially thought to be **331**, seemed to have increased dramatically under these conditions. Subjecting this new product to KOH surprisingly gave **335**. More careful examination of the ^{1}H NMR spectrum of the new product revealed differences compared to the spectrum of authentic **331** and suggested the chloride **336**. Structure **336** was corroborated by HRMS and ^{13}C NMR and further experiments supported this conclusion. When citric acid was used in the neutralization

step, **336** was not produced. Treatment of pure **332** (or **339**) with HCl gave **336** in high yield.

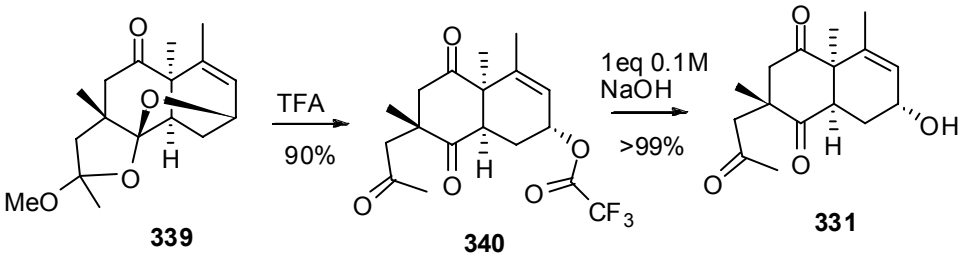
The above experiments suggested that inversion of configuration of the OH group in **332** under acidic conditions was very facile. To take advantage of that chemistry, the plan was to quench the 9-BBN reduction with a strong acid whose conjugate base is a poor nucleophile in hopes of having H_2O act as the nucleophile. Reaction of **332** with $HClO_4$ clearly produced the elimination products **337** and **338** without evidence of **331** (**Scheme 67**).

Scheme 67



Another possibility was to use a strong acid whose conjugate base is a good oxygen-based nucleophile. Treatment of **332** with trifluroacetic acid (TFA) gave **340** in good yield (**Scheme 68**). Treatment of **339** under the same conditions gave **340** in excellent yield. Mild hydrolysis of **340** with NaOH smoothly gave the desired **331**. Reduction of **330** with 9-BBN was readily optimized to give **339** in high yield (1.5 equiv 9-BBN, -10°C; methanol quench; 94% yield). Treatment of **339** with TFA followed by dilute NaOH gave the desired **331** in 90% yield (82% from **330**)

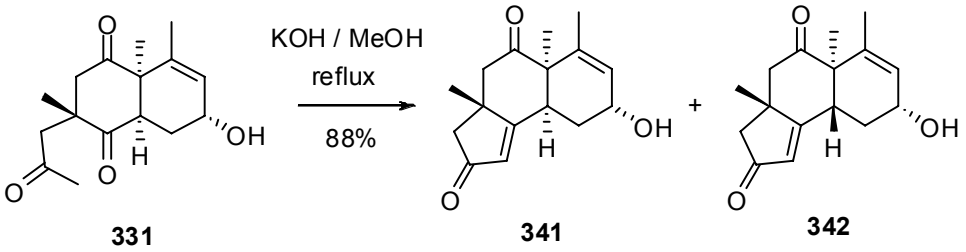
Scheme 68



2.3.4 Formation of the A ring and the *trans* B-C ring junction

With **331** in hand the next step required an aldol cyclization to form the five-membered A ring of the cyathins. Treatment of **331** with KOH in THF under reflux gave the cyclic products **341** and **342** in a 1:1 equilibrium ratio.

Scheme 69



To shift the equilibrium towards the desired *trans*-fused product, reduction of the carbonyl group at C-7 to the β-OH was required. In the resulting product, the *cis*-fused diastereomer **114** is destabilized relative to **115** due to the increased 1,3-diaxial interactions (**Figure 19**).

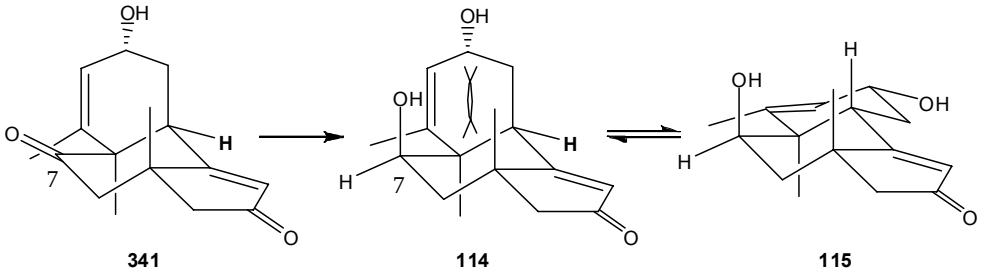
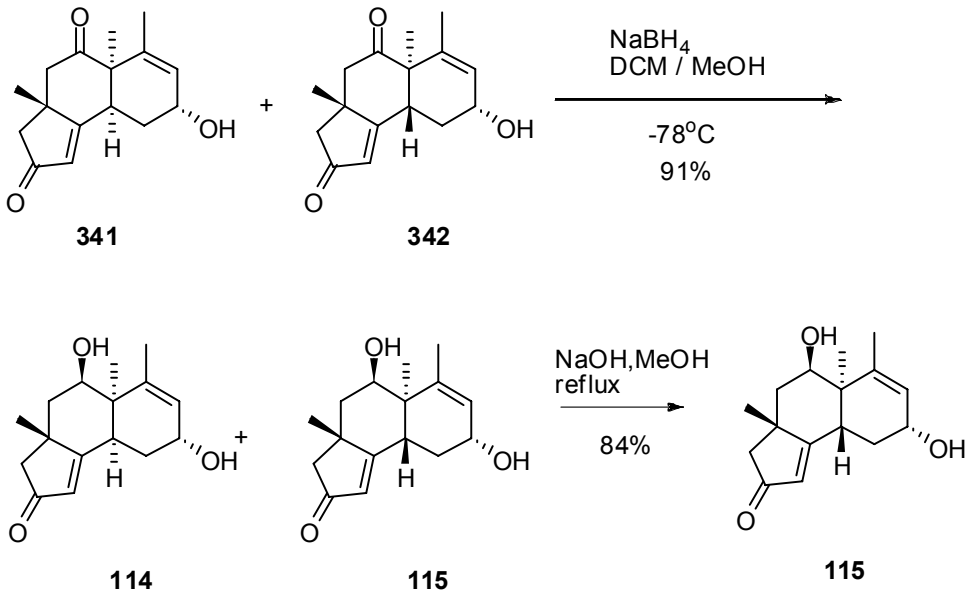


Figure 19. *cis*-fused **114** be destabilized by 1,3-diaxial interactions

Thus, a chemo- and stereoselective reduction of **341** and **342** was required. This was accomplished by treatment with $NaBH_4$ using a procedure previously developed in the group.[51]

Scheme 70



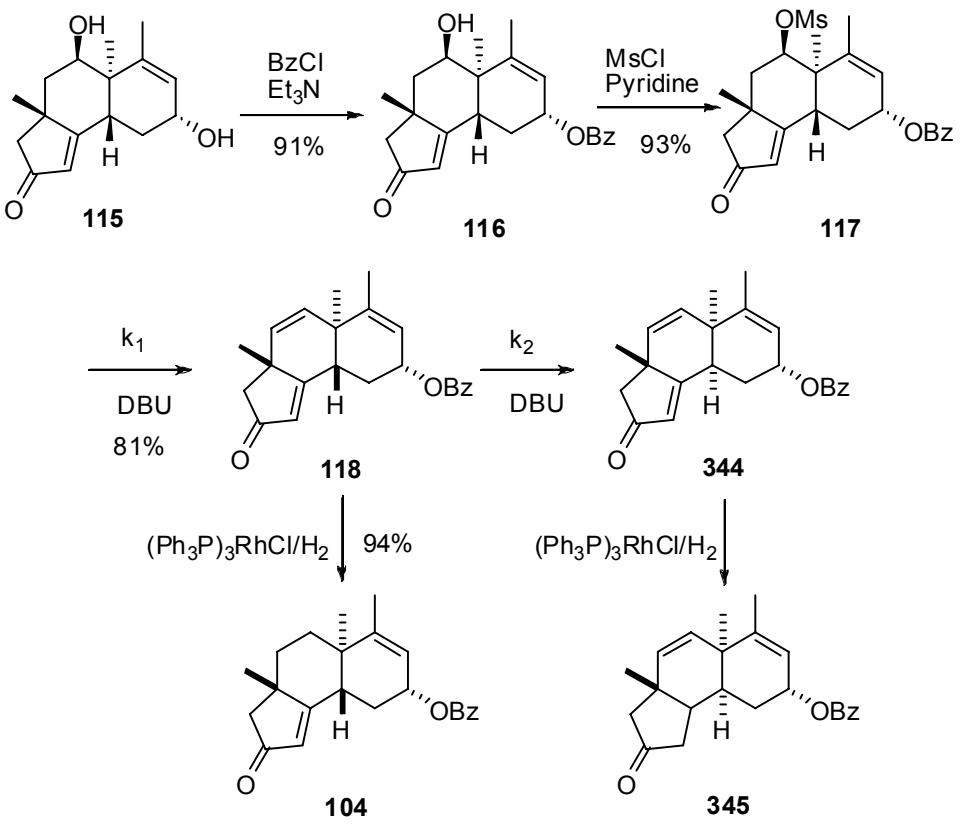
Reaction of the mixture of **341** and **342** with $NaBH_4$ in a 1:1 mixture of CH_2Cl_2 and MeOH at -78 ^oC gave **114** and **115** as the only products (**Scheme 70**). This mixture was heated under reflux in methanolic NaOH for 5 days to afford the desired *trans*-fused **115** in excellent yield.

2.4 Optimized route to the 5-6-7 tricyclic intermediate 103

Transformation of **115** into the 5-6-7 tricyclic ring system present in cyathane diterpenes requires the deoxygenation of the now-redundant C-7 OH group and ring expansion of the cyclohexene by oxidative cleavage of the olefin followed by aldol-type cyclization of the resulting keto-aldehyde.

2.4.1 Deoxygenation of the B ring

Scheme 71



Deoxygenation of the C-7 OH group was previously achieved by a sequential elimination/hydrogenation approach (**Scheme 17**).[46] Diol **115** was converted to **116** via selective benzoylation followed by mesylation

(**Scheme 71**). The elimination of the mesylate **117** required refluxing in toluene for forty hours in the presence of DBU. The product **118** was susceptible to isomerization under these conditions and up to 20% of the *cis* diastereomer **344** was formed during this time period. The two products were difficult to separate by chromatography. The *cis*-isomer **344** is much less reactive towards hydrogenation and could be isolated in pure form from an incomplete hydrogenation of a mixture of **118** and **334**. Under more forcing conditions **344** was reduced to the *cis* ketone **345**.

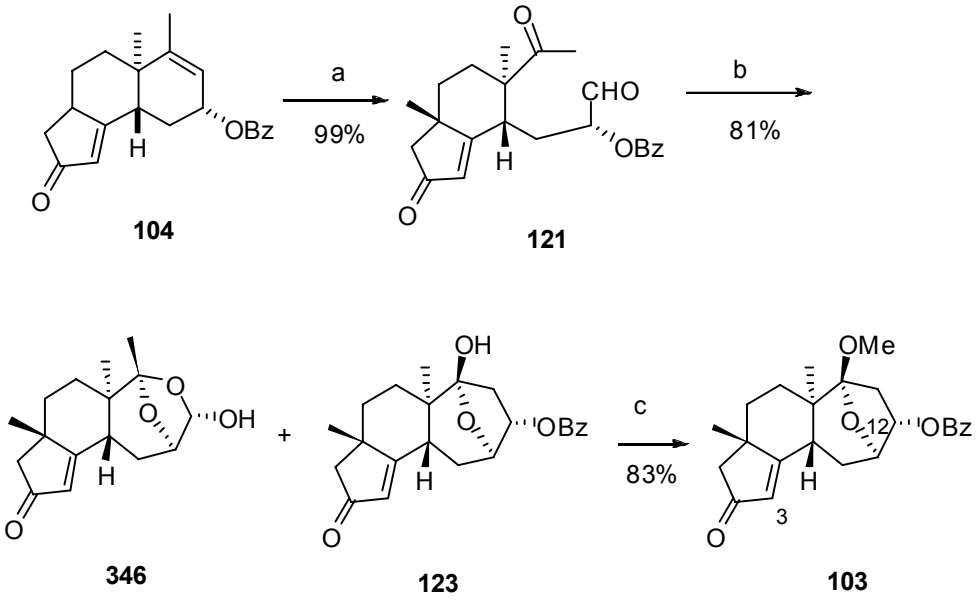
Because isomerization only happens to the elimination product **118**, a simple solution was to stop the reaction at 50% conversion and recycle the recovered **117**. No more than 10% of isomerization of product was detected at this stage. A careful study of the reaction conditions indicated that the product **118** is isomerized much faster in the presence of protonated DBU, the byproduct of the elimination reaction, than with DBU alone. Based on this observation, the reaction was carried out at lower concentration with an excess of DBU. Under these conditions less than 5% isomerization to **344** was detected. The chemoselective hydrogenation of the disubstituted olefin in **118** was achieved efficiently using Wilkinson's catalyst to obtain **104**.

2.4.2 Ring expansion

The next stage of the synthesis involved ring expansion of the cyclohexene. Considerable effort was devoted to optimizing this transformation. As previously,[46] the cyclohexene double bond in **104** was selectively oxidized by treatment with O_3 in presence of Sudan III as an indicator (**Scheme 72**). In the presence of TsOH, the resulting ketoaldehyde **121** underwent aldol cyclization with concomitant 1,2-migration of the benzoyl group to give **123** along with significant quantities (3:1) of a side product **346** derived from simple hydrolysis of the benzoate group in **121**.[46] The cyclization reaction was very sensitive to the presence of water and various conditions (different

acids, solvents, drying protocols) were attempted to improve the yield of **123**. Optimal results were obtained with the use of dry TsOH in dry toluene in the presence of 5 Å molecular sieves at 50 °C, which gave **123** in 80% yield and with very little of the hydrolysis side product (<5%). All of the above work was conducted using a rather old jar (>30 years) of $TsOH \cdot H_2O$ (slightly off-white flakes, Eastman); we were surprised to find that cyclization could not be effected using $TsOH \cdot H_2O$ from a "new" bottle (white crystals, Aldrich). Although the source of this discrepancy is uncertain, after much experimentation we were able to reproduce the cyclization using new $TsOH \cdot H_2O$ with 5% of H_2SO_4. Methylation of **123** by treatment with methyl iodide in the presence of freshly prepared Ag_2O gave **103**, completing the 5-6-7 tricyclic ring system of the cyathins.

Scheme 72



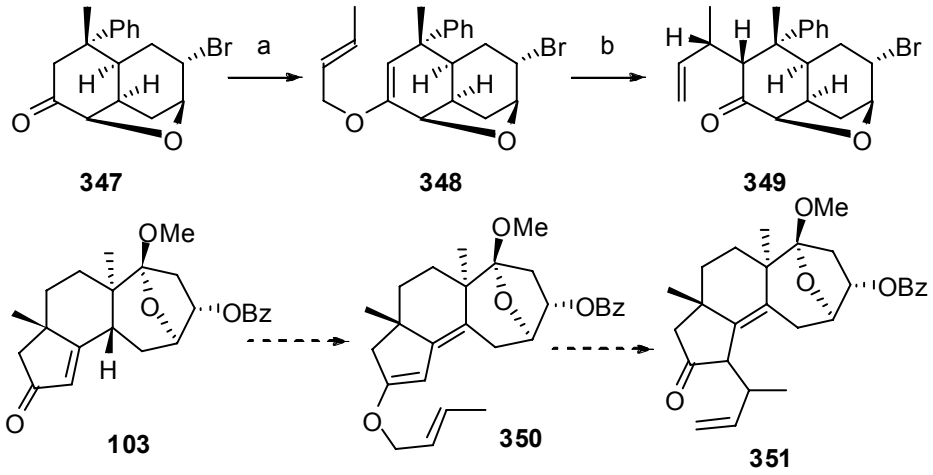
a O_3, Sudan III; b TsOH, toluene, benzene; c Ag_2O, MeI

2.5 Introduction of the isopropyl group

Intermediate **103** possesses the ring system and stereochemistry present in the cyathin diterpenes. Completion of the cyathin skeleton requires introduction of a hydroxmethyl substituent at C-12 and an isopropyl group at C-3. Introduction of an isopropyl group or any branched alkyl group to the alpha position of an enone is always a challenging problem.[148] In the case of **103** the substitution at the beta position of the enone makes this problem even more difficult. Several strategies were attempted.

2.5.1 Claisen rearrangement approach

Scheme 73



a $CH_3CH=CHCH_2OH$, H^+, 50%; b 210 ^oC, 86%

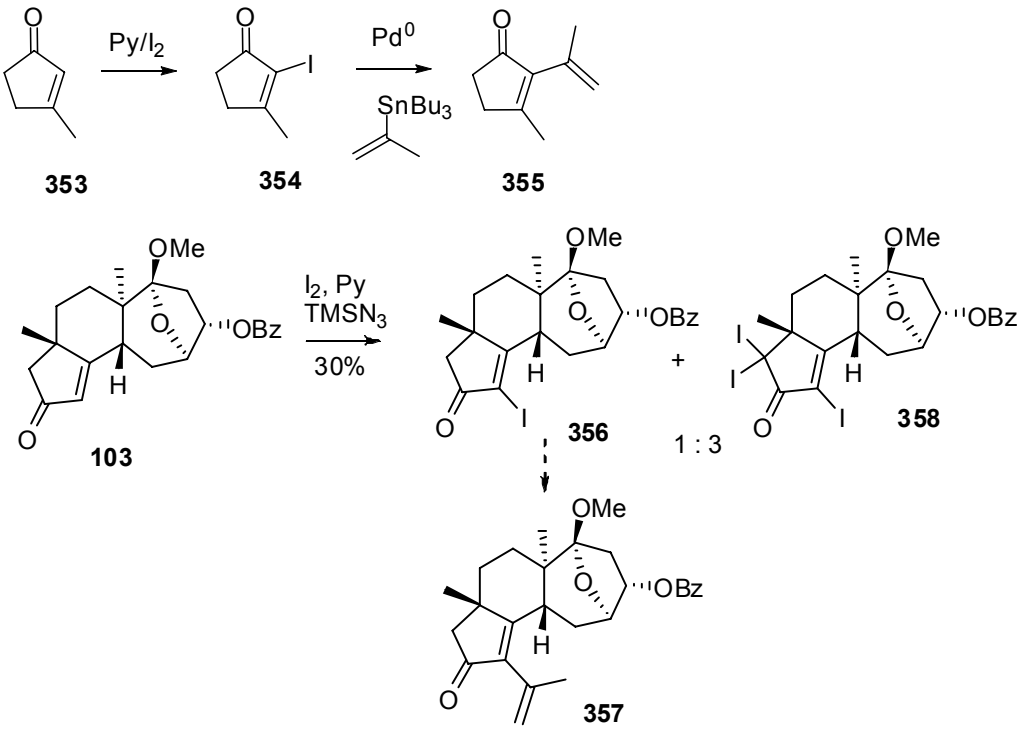
Hopkins reported the introduction of a 1-methyl-2-propenyl subsituent to the α-position of a cycloalkenone via Claisen rearrangement of the derived 2-butenyl enol ether (**Scheme 73**). [149] In principle, a 1-methyl-2-propenyl substituent could be transformed into an isopropyl group by oxidative cleavage of the olefin followed by reduction. In previous work,[47] the enone **103** was converted to the methyl enol ether **124** under acidic conditions (**Scheme 19**). It was speculated that a similar transformation would yield

compound **350**, that in turn could undergo Claisen rearrangement to give the desired ketone **351**. However, under the reported conditions,[149] the enol ether **350** was never detected and only **103** was recovered. Additional experiments with changes in concentration, solvent, and stoichiometry were attempted without success.

2.5.2 Cross-coupling approach

Among the carbon-carbon bond-forming reactions, Pd catalyzed cross coupling reactions have recently gained prominence (Heck,[150] Suzuki,[151] Stille,[152] and Negishi[153,154] reactions). For the synthesis of complex molecules, the Stille coupling is often superior, displaying high selectivity and broad scope.[152,155] Consequently, I considered introducing the isopropyl substituent directly to **103** by a cross-coupling reaction of the corresponding iodide **356** (**Scheme 74**). [76]

Scheme 74

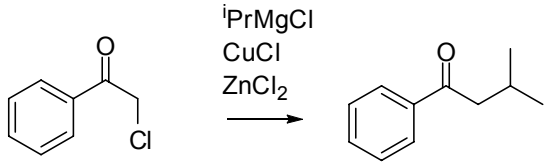


Treatment of cycloalkenones with pyridine/iodine is the most acceptable

and general preparative route to α-iodocycloalkenones.[156] Considerable effort was directed at optimizing this protocol for **103**. However, under various conditions the desired product **356** was not detected. An alternative approach, especially for β-substituted cycloalkenones, uses trimethylsilyl azide as the activating agent to generate a TMS enol ether *in situ*, and this reactive intermediate undergos iodination.[157] Treatment of **103** with trimethylsilyl azide and then with a mixture of iodine and pyridine sequentially in dichloromethane gave a 1:3 mixture of iodide **356** and triiodide **358** in low yield (**Scheme 74**). The amount of **356** obtained by this procedure was too low to permit an investigation of the cross-coupling reaction. However, because the triiodide **358** potentially can be converted to iodide **356**, this approach still remains attractive and further investigation is warranted.

2.5.3 Grignard addition approach

Recently, the Ready[158] group reported a copper-catalyzed reaction of organozinc halides with α-chloroketones, that enables the introduction of primary and secondary alkyl groups adjacent to a ketone carbonyl (e.g., **359** to **360**).

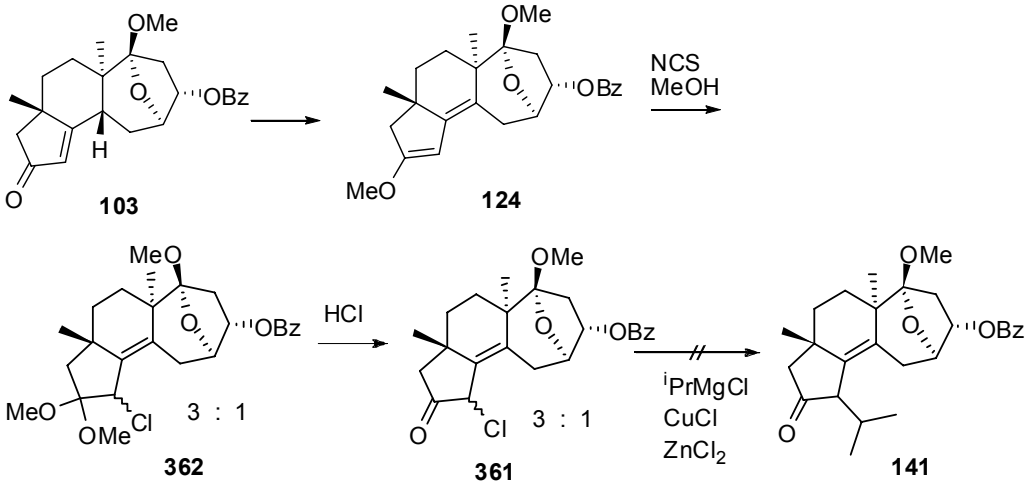


359 **360**

To incorporate this direct alkylation approach into the synthetic route, the preparation of α-chloroketone **361** in reasonable yield was required (**Scheme 76**). The synthesis of **361** started with cohalagenation of the dienol ether **124** with NCS and methanol to give a mixture of **361** and **362**. Treatment of the mixture with aq. HCl gave the desired α-chloroketone **361**

as a 3:1 mixture of two diastereomers. Following the reported protocol, the desired **141** could not be prepared from **361** (under conditions that worked well for **359**). Only the dechlorinated ketone was recovered from the reaction.

Scheme 75

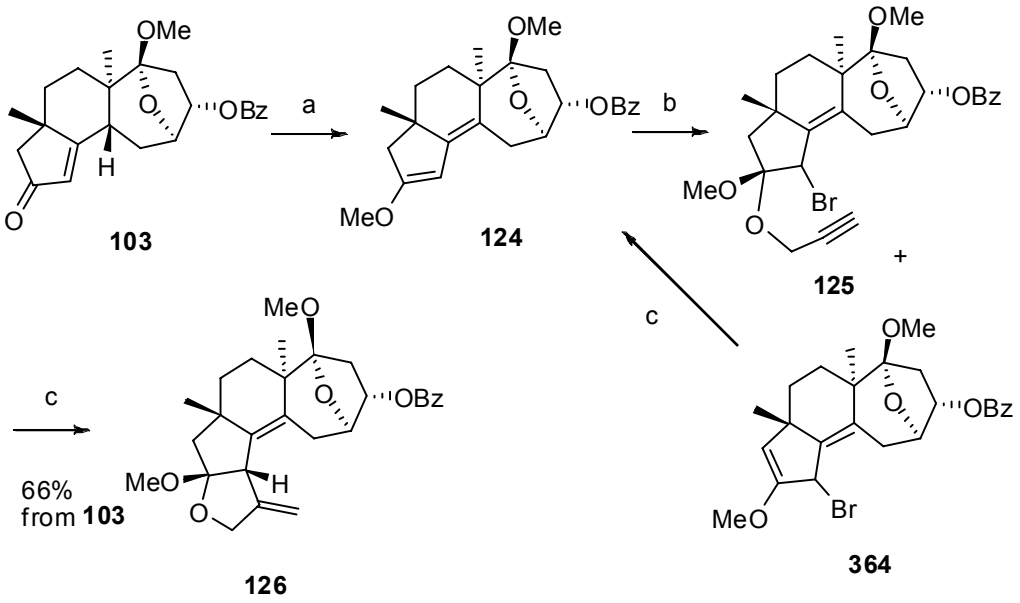


2.5.4 Optimization of the radical cyclization approach

After the Claisen and cross-coupling strategies failed, I decided to optimize the previously developed radical cyclization approach. The ketone **103** was converted to the enol ether **124** upon treatment with trimethyl orthoformate and 3% methanolic HCl (**Scheme 77**). Subjecting compound **124** to propargyl alcohol in presence of NBS at -78 ^{o}C provided the bromo-ketal **125**. Control experiments suggested that the bromo-ketal **125** was not stable to propargyl alcohol at room temperature. The major decomposition product was tentatively assigned structure **364**. Under the subsequent radical cyclization conditions, the side product **364** is converted back to the enol ether **124**. The simple solution is a quick work up including concentration of the crude product from benzene to remove the propargyl

alcohol. The resulting crude bromo-ketal **125** was used in the radical cyclization step without further purification. Treatment of the crude **125** with Ph_3SnH in degassed benzene (0.02 M) under reflux gave **126** in 66% overall yield from **103**.

Scheme 76



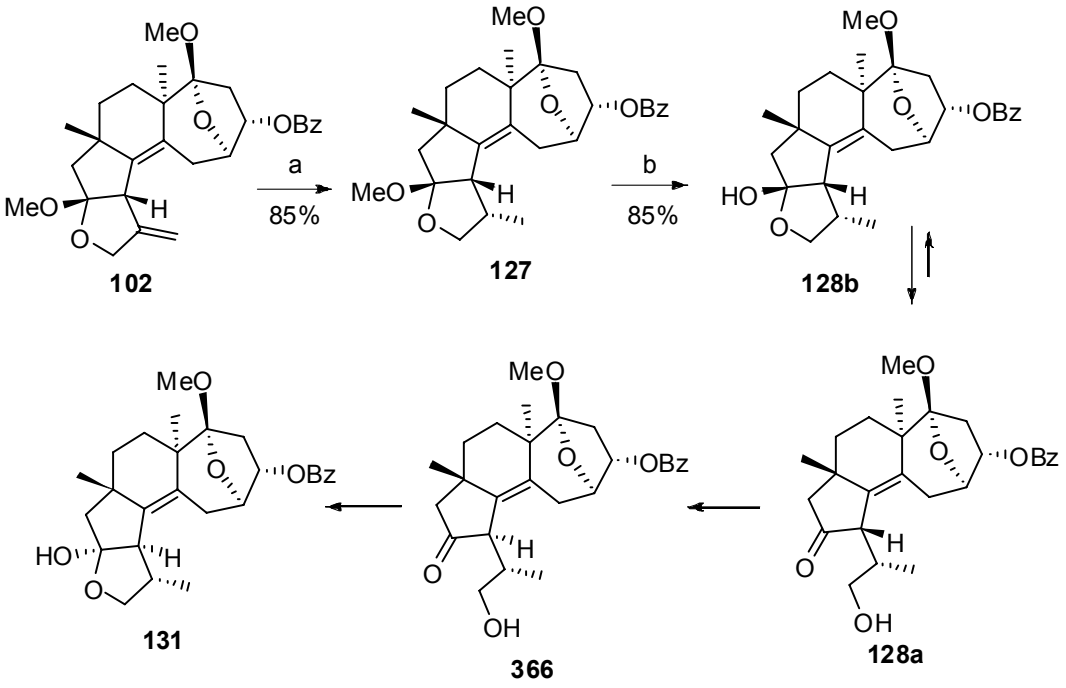
a $HC(OMe)_3$, 3% HCl, MeOH; b Propargyl alcohol, NBS; c Ph_3SnH

Compound **126** possessed the desired isopropyl three carbon unit at the correct position, albeit in a masked form. To complete the total synthesis of a cyathin diterpenoid would require some functional group manipulations on compound **126** in order to unmask the isopropyl group. Direct hydrolysis of **126** under acidic conditions led only to the formation of the energetically favorable furan. Hence, saturation of the exocyclic double bond was required to prevent the aromatization. Hydrogenation of **126** over Pd-C gave **127** in good yield (**Scheme 78**).

Attempted hydrolysis of **127** was difficult because of its facile isomerization to **131**, a compound that proved to be intractable to further desired synthetic transformations (see section 1.4.4 and **Scheme 19**). Hydrolysis of the ketal **127** to the desired **128** was previously achieved by treatment with

pyridinium *p*-toluenesulfonate (PPTS) in aqueous acetone for fourteen days. To shorten this long-term process, a variety of acids were investigated. In most cases, **131** was the only product. Finally, hydrolysis of **127** with Amberlyst in 7.5% aqueous acetone at room temperature for 10 h gave the desired **128** in 85% yield. In $CDCl_3$ solution, **128** was a 1.5:1 mixture of the ring-chain tautomers **128a** and **128b**, respectively.

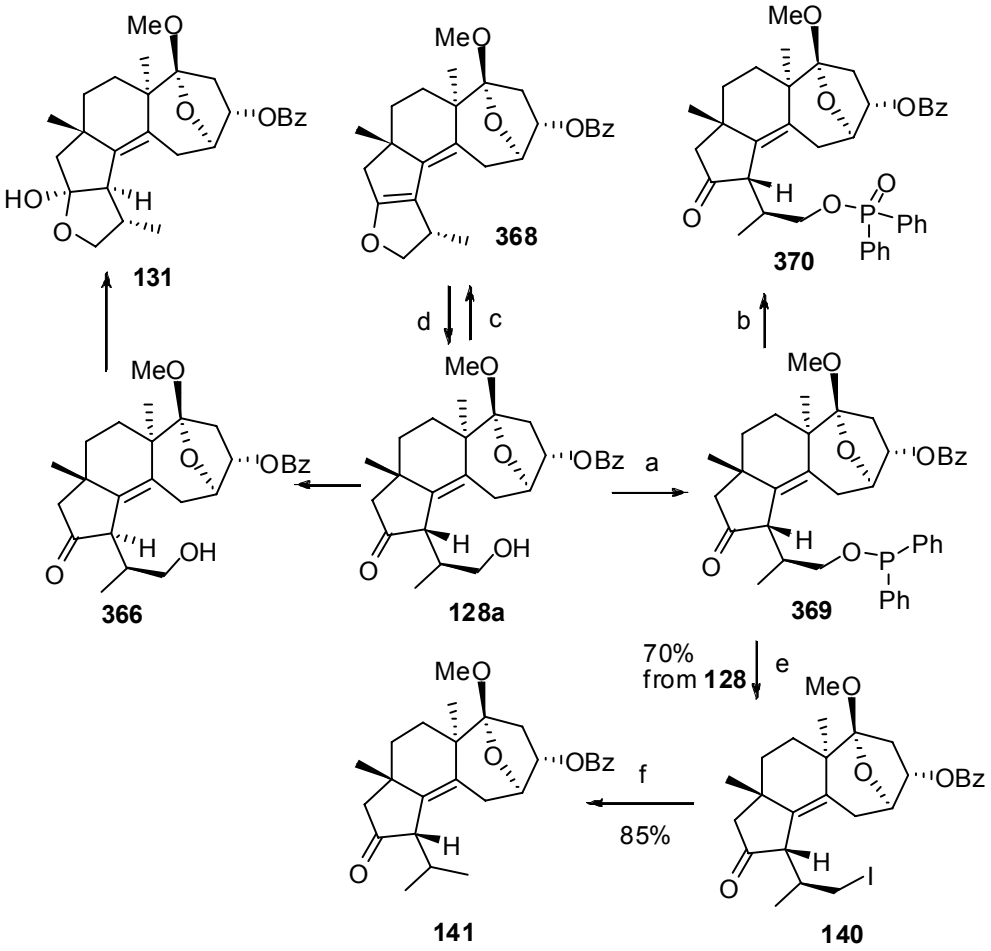
Scheme 77



a. H_2, Pd-C; b. Amberlyst, acetone, H_2O

With compound **128** in hand, it was of interest to pursue derivatization of the hydroxyl functionality that would eventually lead to the desired deoxygenation product. Previous studies had established the feasibility of converting **128** into iodide **140** by reaction with Ph_2PCl followed by I_2 (**Scheme 79**). However this reaction was very capricious and I undertook a detailed study in an effort to optimize the process.

Scheme 78

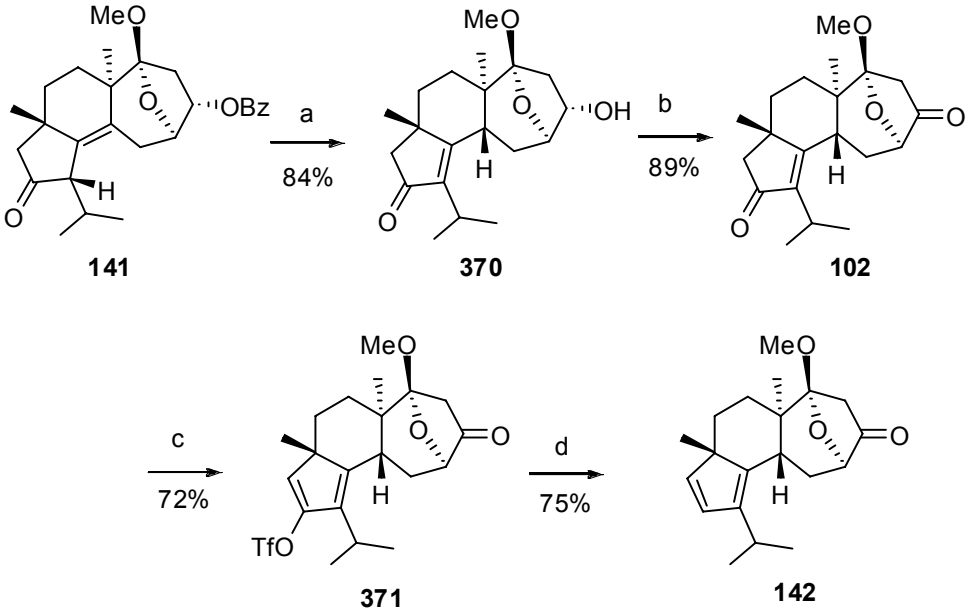


a. $ClPPh_2$, Pyr; b. O_2, H_2O; c. I_2, Pyr, $ClPPh_2$; d. Amberlyst, H_2O, Acetone; e. I_2, Pyr; f. H_2, Pd black, $BaCO_3$

This reaction is highly sensitive to moisture and oxygen. Isomerization product **131** and oxidation product **370** are the two major side products. Treatment of substrate **128** with Ph_2PCl and I_2 simultaneously, gave diene **368** is the only product. This product was also observed in the sequential reaction if the phosphenyation was incomplete. Fortunately, **368** can be converted back to starting material **128** by hydrolysis in acetone. Under optimized conditions, iodide **140** was obtained in 70% yield from **128**. Reduction of **140** with H_2 over Pd-C gave α-isopropylketone **141**.

2.6 Synthesis of cyathin A_3

Scheme 79



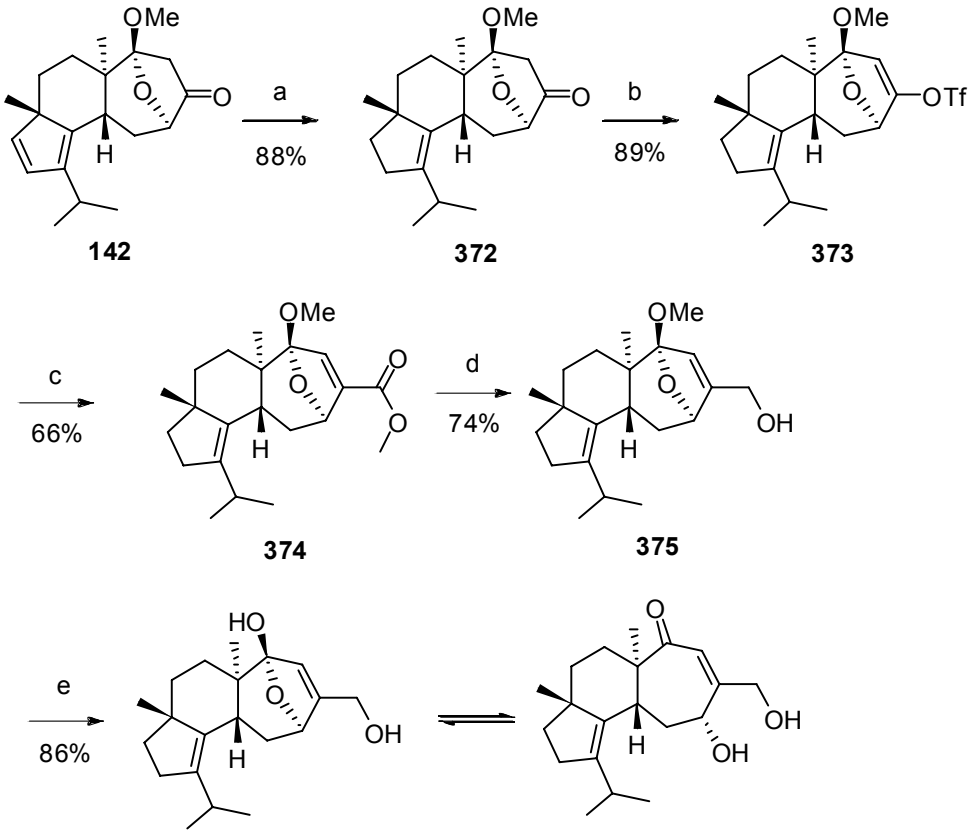
a NaOH/MeOH, reflux; b NMO, TPAP, MS-4A; c Tf_2O, TTBP; d HCO_2H, Et_3N, $Pd(OAc)_2$, DMF, PPh_3

Treatment of **141** with NaOH in MeOH resulted in hydrolysis of the benzoate ester with concomitant isomerization of the double bond into the required position to give **370**. This isomerization reestablished the desired trans 6-7 ring fusion. The presence of the transannular acetal within the seven-membered ring makes the cis-fused diastereomer impossibly strained. To avoid protection and deprotection steps, **370** was directly oxidized to diketone **102** with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine (NMO)[56]. Selective deoxygenation of the cyclopentenone carbonyl was achieved by reaction of **102** with triflic anhydride (Tf_2O) in the presence of 2,6-di-*tert*-butyl-4-methylpyridine[57] to chemoselectively give the dienol triflate, which was reduced to cyclopentadiene **142** by Pd catalyzed reaction with HCO_2H/Et_3N.[159]

Finally, the selective hydrogenation of the diene **142** was achieved by using

Pd-C. Introduction of the vinyl hydroxymethyl group was achieved by Pd catalyzed carbonylation of the vinyl triflate **373** derived from ketone **372** followed by DIBAL-H reduction of the resulting ester **374** to give cyathin A_3 methyl ketal (-)-**375** (50% from **372**). Spectral data (^1H and ^{13}C NMR, $[\alpha]_D$, IR, MS) for (-)**375** closely matched previously reported data[3]. Hydrolysis of **375** to cyathin A_3 **1** (a mixture of hydroxy ketone and hemiacetal tautomers) proceeded readily in THF solution on exposure to aqueous $HClO_4$.

Scheme 80



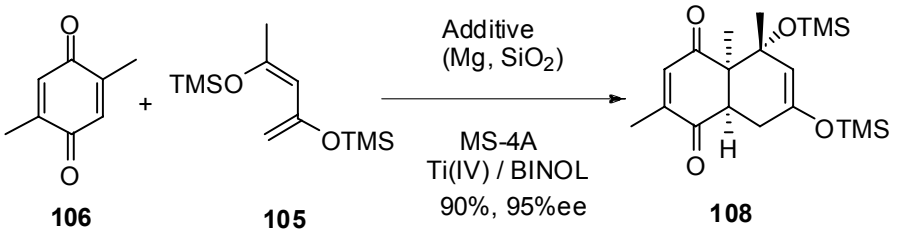
a Pd/C, H_2; b NaHMDS, $PhNTf_2$; c $Pd(PPh_3)_4$, CO, MeOH; d DIBAL-H; e $HClO_4$

2.7 Conclusions

The goal of my thesis research was to establish an enantioselective 2nd

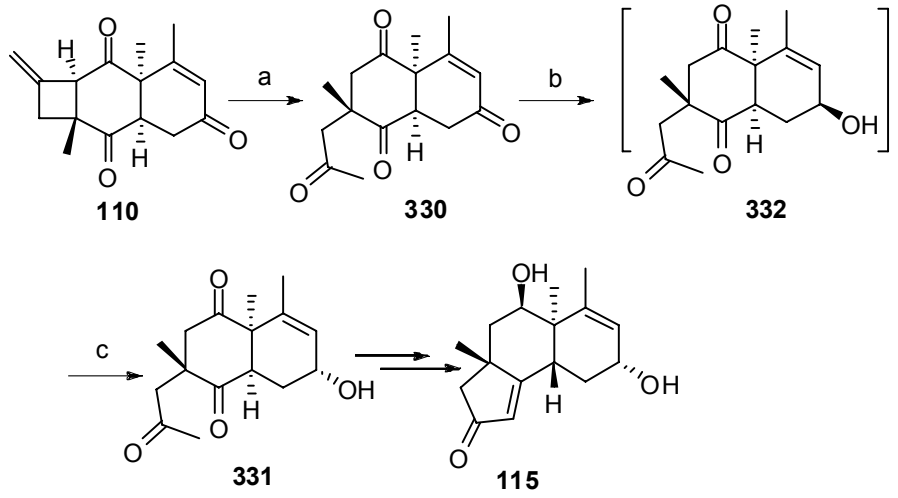
generation synthetic route to cyathane diterpenes. Most of the objectives were achieved:

Objective 1: Develop an enantioselective version of the first Diels-Alder reaction.



The enantioselective Diels-Alder reaction of 2,5-dimethylbenzoquinone (**106**) with Danishefsky type diene (**105**) is effectively catalyzed by Mikami's catalyst modifed by addition of Mg powder and silica gel to give adduct **108** in 90% yield and 95%ee. The absolute configuration of the Diels-Alder adduct **108** was determined by the X-ray analysis of the Mosher's ester **325.** Thus, the preparation of 108 with the desired absolute configuration for synthesis of cyathins requires the catalyst derived from (*R*)-BINOL. This is the first example of an enantioselective Diels-Alder reaction both of quinone (**106**) and of a Danishefsky-type diene (e.g. **105**).

Objective 2: Establish a more direct route from 110 to 115.

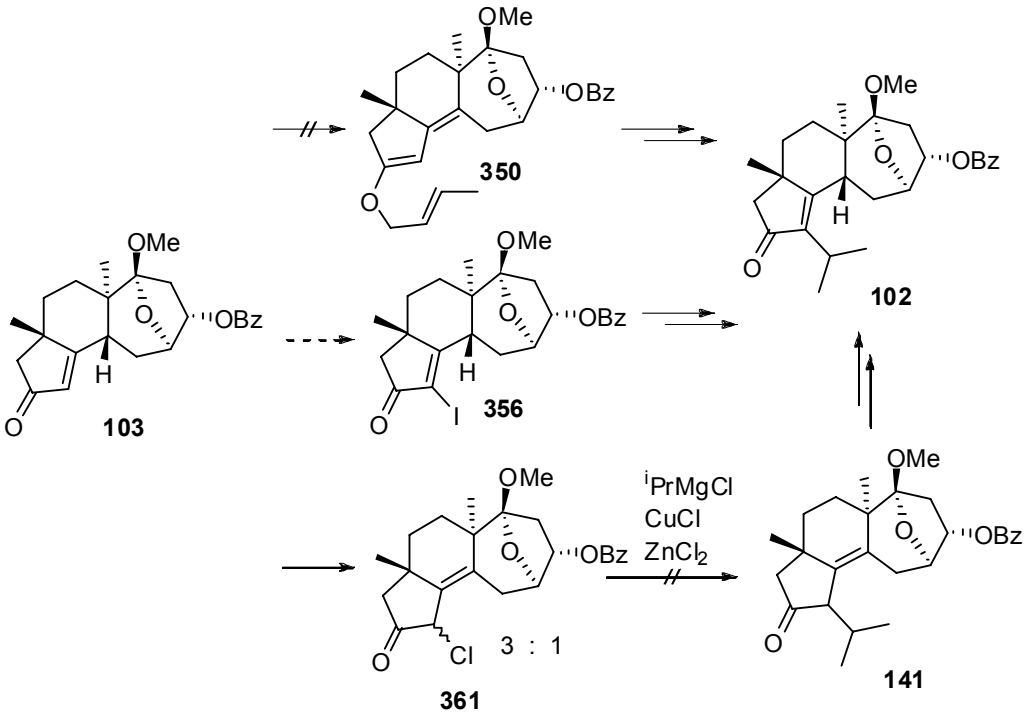


a) $Hg(ClO_4)_2$, acetone:H_2O=1:3; b) 9-BBN; c) i. TFA, ii.NaOH.

The more direct transformation from **110** to **330**, involving a Markovnikoff

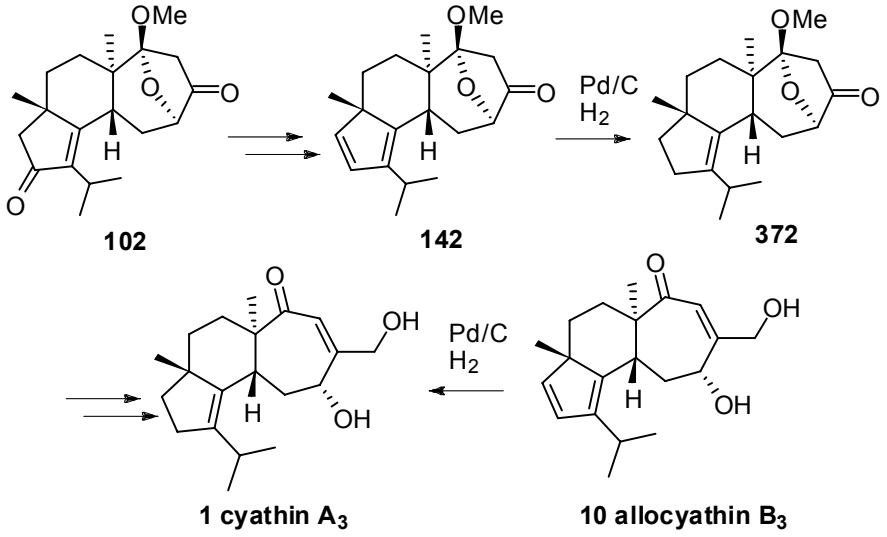
hydration of the exocyclic alkene followed by a retro-aldol fragmentation of the cyclobutane moiety, was accomplished by oxymercuration. Selective reduction of **330** was achieved with 9-BBN. The configuration of the initially formed β-OH product **332** was inverted on workup with trifluoroacetic acid and sodium hydroxide to give the desired α-OH product **331**.

Objective 3: Develop a more direct approach to introduce the isopropyl group.

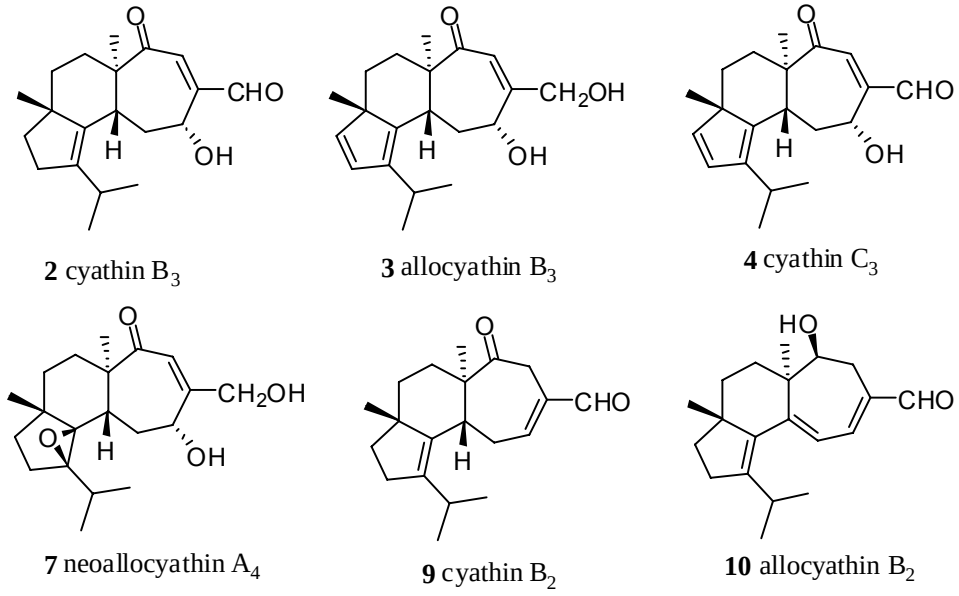


Attempts to introduce the isopropylgroup via Claisen rearrangement approach and cross-coupling approach was not successful because I was unable to prepare either the enol ether **350** or the iodide **356**. Following the reported protocol, the desired **141** could not be prepared from **361**. Only the dechlorinated ketone was recovered from the reaction. Consequently, the previously developed route to **141** via radical cyclization was extensively optimized.

Objective 4: Establish a synthetic route to cyathin A_3



Selective reduction of conjugated diene **142** was achieved by a mild hydrogenation catalyzed with palladium on carbon and this method potentially can be used to convert allocyathin B_2 (**10**) into cyathin A_3 (**1**). An enantioselective total synthesis of (-)-cyathin A_3 (**1**) has been achieved in 28 steps (0.65% overall yield).

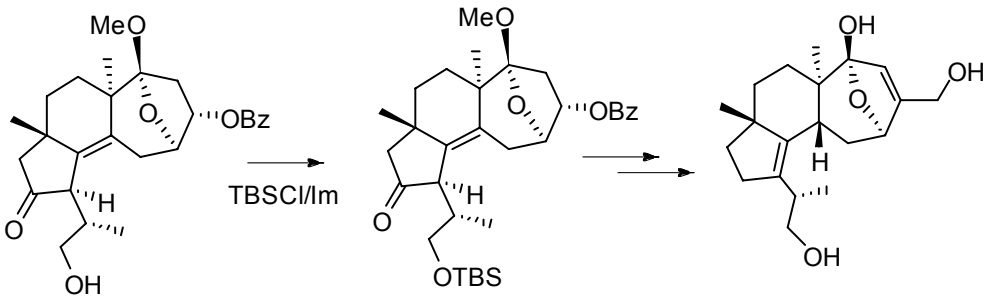


2 cyathin B_3 **3** allocyathin B_3 **4** cyathin C_3

7 neoallocyathin A_4 **9** cyathin B_2 **10** allocyathin B_2

Because cyathin A_3 (**1**) is easily transformed into cyathin B_3 (**2**), allocyathin

B_3 (**3**), cyathin C_3 (**4**), neoallocyathin A_4 (**7**), cyathin B_2 (**9**) and allocyathin B_2 (**10**), this route also constitutes a formal synthesis of these natural products. Now envisioned in our laboratory is the development of a new access to cyathin A_4 (**5**), which is surmised to be possible via an intermediate prepared in this synthesis (e.g. **128** and **376**).



128 **376** **5** cyathin A_4

3. Experimental

3.1 General Methods

All solvents were distilled prior to use. Anhydrous solvents were distilled under an argon atmosphere as follows: Tetrahydrofuran (THF) and ether from benzophenone sodium ketyl; CH_2Cl_2 and toluene from CaH_2; MeOH from $Mg(OMe)_2$; Et_3N and $TiCl_4$ were distilled from CaH_2. All experiments involving air- and/or moisture-sensitive compounds were conducted in ovendried round-bottom flasks capped with rubber septa, and attached via a needle and connecting tubing to an argon manifold equipped with mercury bubbler (ca. 5 mm positive pressure of argon). Low temperature baths were ice/water (0°C) and $CO_{2(s)}$/acetone (-78°C). Reaction temperatures refer to that of the bath.

Preparative thin layer chromatography (PTLC) was carried out on glass plates (20×20 cm) precoated (0.25 mm) with silica gel 60 F_{254}. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by cutting a 1 cm vertical strip from the plate and wetting this strip with a solution of phosphomolybdic acid (5%) containing a trace of ceric sulfate in aqueous sulfuric acid (5% v/v), followed by charring on a hot plate.

Concentration refers to removal of volatiles at water aspirator pressure on a rotary evaporator followed by evacuation at 0.5-1 torr obtained with a vacuum pump. Unless otherwise noted, all reported compounds were homogeneous by thin layer chromatography (TLC) and by NMR. Flash

column chromatography (FCC) was performed according to Still[160] *et al*. with Merck Silica Gel 60 (40-63 μm). Medium pressure chromatography (MPC) was performed as reported by Taber.[161] Dry flash column chromatography was performed according to Harwood.[162] All mixed solvent eluents are reported as v/v solutions.

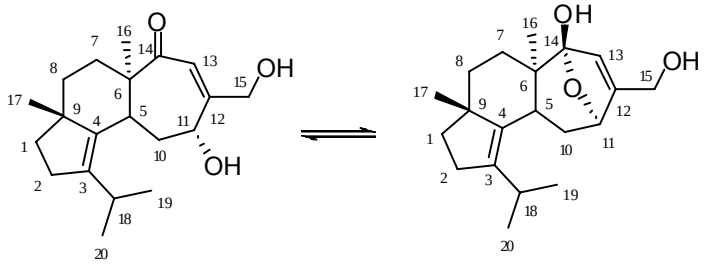
High resolution mass spectra (HRMS) and low resolution mass spectra (LRMS) were obtained on a VG 70E double focussing high resolution spectrometer; only partial data are reported. Electron impact (EI) ionization was accomplished at 70 eV and chemical ionization (CI) at 50 eV with ammonia as the reagent gas; only partial data are reported. Infra red (IR) spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. Unless otherwise noted, NMR spectra were measured in $CDCl_3$ solution at 500 MHz for ^1H NMR and 125 MHz for ^{13}C NMR. Signals due to the solvent (^{13}C NMR) or residual protonated solvent (^1H NMR) served as the internal standard: $CDCl_3$ (7.27 δ_H, 77.23 δ_C); CD_3OD (3.31 δ_H, 49.15 δ_C); C_6D_6 (7.16 δ_H, 128.39 δ_C). The ^1H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ap (apparent); the list of coupling constants (*J*) corresponds to the order of the multiplicity assignment. In keeping with the typical digital resolution obtained (ca. 0.25Hz/pt), couplings constants (*J*) are reported to the nearest 0.5 Hz. The ^1H NMR assignments were made on the basis of chemical shift and multiplicity and were confirmed, where necessary, by 1D homonuclear decoupling, 2D $^1H/^1H$ homonuclear shift correlation (COSY) and/or 1D NOE experiments. The ^{13}C NMR assignments were made on the basis of chemical shift and multiplicity as determined by *J*-modulation and were confirmed, where necessary, by 2D $^1H/^{13}C$ one bond correlation (HSQC) and 2D $^1H/^{13}C$ multiple bond correlation (HMBC) experiments.

Ag_2O,[163] $TiCl_2(O^iPr)_2$,[164,165] quinone **106**[48,49] and diene **105**[50] were prepared by known procedures. All other reagents were commercially available and, unless otherwise noted, were used as received.

3.2 Experimental procedures and spectral data

(3a*R*,5a*S*,9*S*,10a*S*)-3,3a,4,5,5a,9,10,10a-Octahydro-9-hydroxy-8-(hydroxymethyl)-3a,5a-dimethyl-1-(1-methylethyl) cyclohept[*e*]inden-6(2*H*)-one (1a)

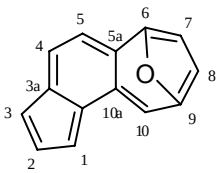
(3a*R*,5a*S*,6*S*,9*S*,10a*S*)-2,3,3a,4,5,5a,6,9,10,10a-Decahydro-6-hydroxy-3a,5a-dimethyl-1-(1-methylethyl)-6,9-epoxycyclohept[*e*]indene-8-methanol (1b) (Cyathin A_3) [a]



1a **1b**

Cyathin A_3 methyl ketal **375** (7 mg) was dissolved in THF (1 mL) and 1M aq. perchloric acid (70 μL) was added and the solution was stirred at room temperature for 5 days after which time TLC showed only the desired **1**. The solution was diluted with saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2. Evaporation of the solvent gave cyathin A_3 (**1**, 5.5 mg, 89%) as an oil. ($[\alpha]_D^{27}$ = -160; *c* = 0.5, MeOH) (lit.[3] $[\alpha]_D$ = -155; *c* = 0.26, MeOH)

IR (KBr) ν_{max} (cm^{-1}): 3394, 1734, 1606.

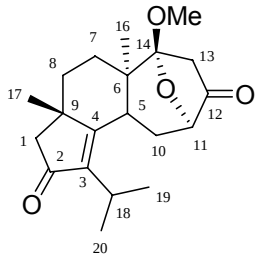


[a] The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left. Spectral assignments are according to the cyathin numbering system as indicated on the structure shown above.

LRMS (EI), *m/z* (relative intensity): 318 ($[M]^+$, 4), 303 (9), 191 (14), 175 (12), 97 (36), 69 (100).

HRMS *m/z* calcd. for $C_{21}H_{30}O_3$: 318.2195; found: 318.2196 (EI).

(3a*R*,5a*S*,6*S*,9*S*,10a*S*)-3,3a,4,5,5a,6,7,9,10,10a-Decahydro-6-methoxy-3a,5a-dimethyl-1-(1-methylethyl)-6,9-epoxycyclohept[*e*]indene-2,8-dione (102) [a]

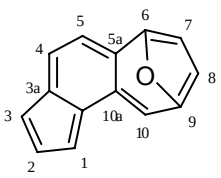


102

TPAP (25 mg, 0.071 mmol) was added to a stirred suspension of powdered 4 Å molecular sieves (100 mg), *N*-methylmorpholine oxide (20 mg, 0.17 mmol), and alcohol **370** (18 mg, 0.054 mmol) in dry CH_3CN (4 mL). After 2 h, the mixture was concentrated and fractionated by FCC (20% ethyl acetate in hexane) to give **102** (16 mg, 89%). ($[\alpha]_D^{27}$ = -120; *c* = 1.1, CH_2Cl_2)

IR (KBr) ν_{max} (cm^{-1}): 1740, 1717

.



[a] The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left. Spectral assignments are according to the cyathin numbering system as indicated on the structure shown above.

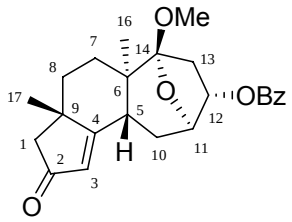
^{1}H NMR (500 MHz $CDCl_3$) δ: 4.35 (1H, m, HC-11), 3.42 (3H, s, H_3C-15), 2.94 (1H, qq, *J* = 7, 7 Hz, HC-18), 2.70~2.80 (2H, m, HC-5, 13), 2.56 (1H, d, *J* = 18.5 Hz, HC-13), 2.47 (1H, ddd, *J* = 4, 13.5, 13.5 Hz, HC-10), 2.22 (1H, d, *J* = 18.5 Hz, HC-1), 2.16 (1H, d, *J* = 18.5 Hz, HC-1), 1.97 (1H, ddd, *J* = 2, 4, 13 Hz, HC-10), 1.25~1.85 (4H, m, H_2C-7, 8), 1.23 (3H, d, *J* = 7 Hz, H_3C-19/20), 1.20 (3H, d, *J* = 7 Hz, H_3C-19/20), 1.20 (3H, s, H_3C-16/17), 1.09 (3H, s, H_3C-16/17).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 215.2, 208.3, 173.2, 143.5, 109.5, 80.9, 52.7, 49.8, 45.5, 39.9, 39.3, 39.2, 36.0, 28.2, 27.9, 26.6, 26.1, 20.5, 20.2, 12.8.

LRMS (EI), *m/z* (relative intensity): 332 ($[M]^+$, 30), 204 (100), 189 (51), 176 (26), 162 (28), 149 (24), 127 (12), 114 (13).

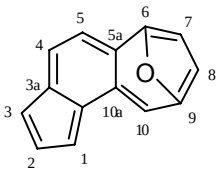
HRMS *m/z* calcd. for $C_{20}H_{28}O_4$: 332.1988; found: 332.1984 (EI).

(3a*R*,5a*S*,6*S*,8*R*,9*S*,10a*S*)-8-(Benzoyloxy)-3a,4,5,5a,6,7,8,9,10,10a-decahydro-6-methoxy-3a,5a-dimethyl-6,9-epoxycyclohept[*e*]inden-2(3*H*)-one (103) [a]



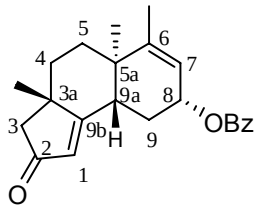
103

Freshly prepared Ag_2O[163] (500 mg, 2.16 mmol) was added to a stirred solution of **123** (702 mg, 1.77 mmol) in MeI (10 mL). After 48 h, the reaction mixture was diluted with ethyl acetate and filtered through Celite. The combined filtrate and washings were concentrated and fractionated by FCC (20% ethyl acetate in hexane) to give **103** (569 mg, 81%). Spectral data for **103** closely matched that reported previously.[46⊥] ($[\alpha]_D^{27}$ = -120; *c* = 1.0, CH_2Cl_2)



[a] The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left. Spectral assignments are according to the cyathin numbering system as indicated on the structure shown above.

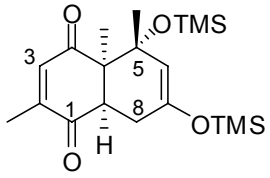
(3a*R*,5*S*,5a*S*,8*S*,9a*S*)-8-(Benzoyloxy)-3,3a,4,5,5a,8,9,9a-octahydro-3a,5a,6-trimethyl-2*H*-benz[*e*]inden-2-one (104)



104

A solution of **118** (1.22 g, 3.48 mmol) and $(Ph_3P)_3RhCl$ (576 mg, 0.623 mmol) in degassed benzene (60 mL) was stirred under a H_2 atmosphere (ca. 3 bar) for 72 h. The mixture was concentrated and fractionated by FCC (30% ethyl acetate in hexane) to give **104** (1.14 g, 94%). Spectral data for **104** closely matched that reported previously.[46] ($[\alpha]_D^{27}$ = -67; *c* = 1.1, CH_2Cl_2)

(4a*R*,5*R*,8a*R*)-4a,5,8,8a-Tetrahydro-2,4a,5-trimethyl-5,7-bis[(trimethylsilyl)oxy]-1,4-naphthalenedione (108)

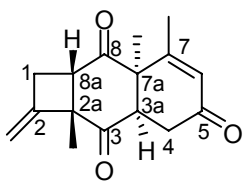


108

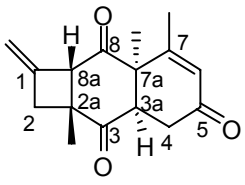
To 4Å molecular sieves (Aldrich, 5-6% H_2O, particle size 2-3μ, 8.0 g) was added a solution of (*R*)-2,2'-dihydroxy-1,1'-binaphthyl (114 mg, 0.40 mmol) in DCM (20 mL) and a solution of $TiCl_2(OiPr)_2$ in toluene (0.30 M; 1.3 mL, 0.4 mmol) at room temperature. The reddish brown reaction mixture was stirred for 1 h and then a solution of 2,5-dimethyl-p-benzoquinone (**106**; 1.0

g, 7.3 mmol) in CH_2Cl_2 (10 mL) was added. After 1 h at room temperature, 2,4-bistrimethylsilyoxy-1,3-pentadiene (**105** as a 1:1 mixture of stereoisomers; 16 g, 65 mmol), magnesium powder (80 mg) and silica gel (EMD, 230-400 mesh powder, 160 mg) were added. The reaction mixture was concentrated to remove all the DCM. The remaining mixture was stirred at room temperature until complete conversion of **106** was indicated by TLC [deactivated silica gel (Et_3N), hexane:EtOAc 4:1] (ca. 24h). The reaction mixture was diluted with hexane (20 mL) and Et_3N (1 mL). After stirring for 0.5 h at room temperature, the reaction mixture was filtered through a Celite pad. The filtrate was concentrated to dryness and the residue fractionated by bulb to bulb distillation (60 ^oC/0.025 torr) to remove the volatile diene, and leave **108** (2.8 g; ca. 95 % purity; ca 95 % yield; 93% ee). A total of 75 g of **108** was prepared from several similar experiments (1-5 g of **106**). Spectral data for **108** closely matched that reported previously for racemic material.[50] The ee of **108** was determined by ^1H NMR analysis of hydrolyzed product **297** (see page 129).

(2a*R*,3a*S*,7a*S*,8a*R*)-1,2,2a,3a,7a,8a-Hexahydro-2a,7,7a-trimethyl-2-methylenecyclobuta[*b*]naphthalene-3,5,8(4*H*)-trione (109)
(2a*R*,3a*R*,7a*R*,8a*S*)-1,2,2a,3a,7a,8a-Hexahydro-2a,7,7a-trimethyl-1-methylenecyclobuta[*b*]naphthalene-3,5,8(4*H*)-trione (110)



109

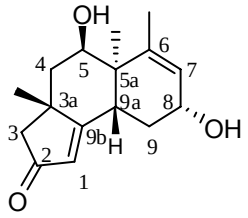


110

Trifluoroacetic acid (1 mL) was added to a stirred solution of the crude photoadducts **327** (10 g) and MeOH (20 mL) in CH_2Cl_2 (180 mL). After 2 h,

toluene (5 mL) was added and the mixture was concentrated to give crude product (6.8 g; **110** : **109** was 3:1 by ^{1}H NMR) that was purified by FCC (50% ethyl acetate in hexane) to give a 3:1 mixture of **110** and **109**, respectively, (5.3 g, 85% from **327**). With similar experiments, a total of 88 g of **327** was converted to 46 g of **109** and **110**. Spectral data for the mixture of **110** and **109** closely matched that reported previously.[50]

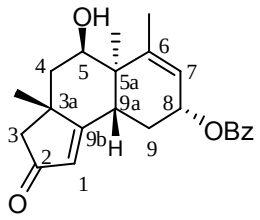
(3a*S*,5*R*,5a*R*,8*S*,9a*R*)-3,3a,4,5,5a,8,9,9a-Octahydro-5,8-dihydroxy-3a,5a,6-trimethyl-2*H*-benz[*e*]inden-2-one (115)



115

The crude 1:1 mixture of diols **343** and **115** (2.16 g) obtained by $NaBH_4$ reduction of the mixture of diones **341** and **342** was taken up in MeOH (150 mL) and NaOH (2 g, 50 mmol) was added and the resulting solution was heated under reflux for 5 days. The cooled reaction mixture was made slightly acidic (pH 6) by addition of 6 N HCl aq. and then $NaHCO_3$ (2 g) was added. The mixture was concentrated to dryness and the resulting solid was extracted with 30% MeOH in CH_2Cl_2 (×3). Concentration of the combined extracts provided **115** (1.82 g, 84%). ($[\alpha]_D^{27}$ = -110; *c* = 0.9, CH_2Cl_2). The spectral data for **115** closely matched that reported previously.[50]

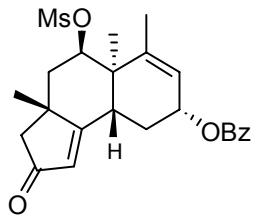
(3a*R*,5*S*,5a*S*,8*S*,9a*S*)-8-(Benzoyloxy)-3,3a,4,5,5a,8,9,9a-octahydro-5-hydroxy-3a,5a,6-trimethyl-2*H*-benz[*e*]inden-2-one (116)



116

PhCOCl (2.3 mL, 2.8 g, 20 mmol), Et_3N (4.6 mL, 3.3 g, 33 mmol), and DMAP (92 mg, 0.75 mmol) were added to a solution of **115** (1.82 g, 6.94 mmol) in CH_2Cl_2 (80 mL). The reaction mixture was kept at 4 °C for 16 h and then MeOH (20 mL) was added. After 30 min, the solution was concentrated and the resulting oil was fractionated by MPC (eluting first with CH_2Cl_2 then with 75% ethyl acetate in hexane) to give **116** (2.22 g, 91%). Spectral data for **116** closely matched that reported previously.[46] ($[\alpha]_D^{27}$ = -110; *c* = 1.1, CH_2Cl_2)

(3a*R*,5*S*,5a*S*,8*S*,9a*S*),8-(Benzoyloxy)-3,3a,4,5,5a,8,9,9a-octahydro-3a,5a,6-trimethyl-5-[(methylsulfonyl)oxy]- 2*H*-benz[*e*]inden-2-one (117)

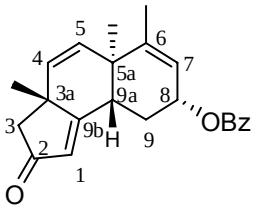


117

Methanesulfonyl chloride (3.6 mL, 5.2 g, 44 mmol) was added over 15 h via a syringe pump to a stirred solution of **116** (2.22, 6.06 mmol) in dry pyridine

(200 mL) at 50 °C under argon. The mixture was concentrated from toluene and then diluted with ethyl acetate, and washed sequentially with dilute aq. HCl, satd. $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (25% ethyl acetate in hexane) to give **117** (2.53 g, 93%). ($[\alpha]_D^{27}$ = -46; *c* = 1.3, CH_2Cl_2) Spectral data for **117** closely matched that reported previously.[46]

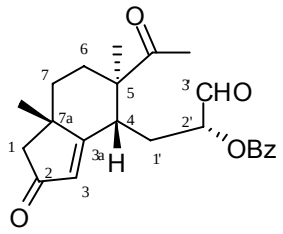
(3a*R*,5a*R*,8*R*,9a*R*)-8-(Benzoyloxy)-3,3a,5a,8,9,9a-hexahydro-3a,5a,6-trimethyl-2H-benz[*e*]inden-2-one (118)



118

Freshly distilled DBU (13 mL, 13 g, 87 mmol) was added to a stirred solution of **117** (2 g, 4.5 mmol) in toluene (500 mL) under argon and the mixture was heated under reflux. Reaction progress was monitored by TLC (50% ethyl acetate in hexane) and after 30–40 h, **117** was no longer present. The mixture was diluted with ethyl acetate and washed sequentially with dilute aq. HCl, satd. $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (30% ethyl acetate in hexane) to give **118** as a colorless oil (1.27 g, 81%). Spectral data for **118** closely matched that reported previously.[46]

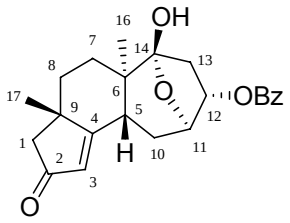
(α*R*,4*R*,5*R*,7a*S*)-5-acetyl-α-(Benzoyloxy)-2,4,5,6,7,7a-hexahydro-5,7a-dimethyl-2-oxo-1*H*-Indene-4-propanal (121)



121

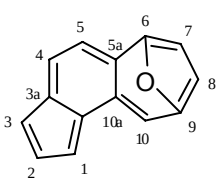
A stream of ozone in air was bubbled through a solution of **104** (841 mg, 2.40 mmol) and Sudan III (1 to 2 mg) in 10% methanolic dichloromethane (300 mL) at –78 °C until the red color was discharged. Argon was bubbled through the solution for 20 min (to remove excess O_3) and then pyridine (0.3 mL) and dimethyl sulfide (1.5 mL) were added and the solution kept at 4 °C (refrigerator) for 16 h. The mixture was concentrated from xylene (to remove pyridine and dimethyl sulfoxide) to provide essentially homogeneous ketoaldehyde **121** (918 mg, 99%). Spectral data for **121** closely matched that reported previously.[46]

(3a*R*,5a*S*,6*S*,8*R*,9*S*,10a*S*)-8-(Benzoyloxy)-3a,4,5,5a,6,7,8,9,10,10a-decahydro-6-hydroxy-3a,5a-dimethyl-6,9-epoxycyclohept[*e*]inden-2(3*H*)-one (123)



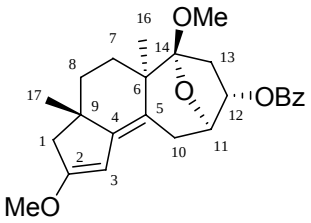
123

A solution of the ketaoaldehyde **121** (918 mg, 2.42 mmol) in benzene (450 mL) was dried by concentration to a volume of ca. 300 mL via distillation under argon. Activated molecular sieves 5 Å (13.5 g; ca. 210 pellets) were added to this solution. A suspension of p-toluenesulfonic acid monohydrate (918 mg, 5.33 mmol) in toluene (240 mL) was heated under reflux in a modified Dean–Stark trap containing activated 5 Å molecular sieves. After 45 min, the resulting dry TsOH solution was allowed to cool to room temperature and then was added to the above solution of ketoaldehyde **121** and the reaction mixture was heated to 40 °C. After 48 h without stirring, the mixture was allowed to cool to room temperature and $NaHCO_3$ (9 g) was added. After stirring for 20 min, the mixture was diluted with ethyl acetate (300 mL) and filtered. The combined filtrate and washings (20% MeOH in CH_2Cl_2) were concentrated and fractionated by FCC (30%–50% ethyl acetate in hexane) to give **123** (702 mg, 76.5 %). Spectral data for **123** closely matched that reported previously.[46]



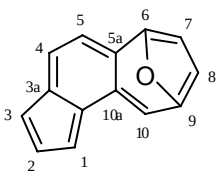
NOTE: The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left. Spectral assignments are according to the cyathin numbering system as indicated on the structure shown above.

(3a*R*,5a*S*,6*S*,8*R*,9*S*)-3,3a,4,5,5a,6,7,8,9,10-decahydro-2,6-dimethoxy-3a,5a-dimethyl-6,9-epoxycyclohept[*e*]inden-8-ol benzoate (124)



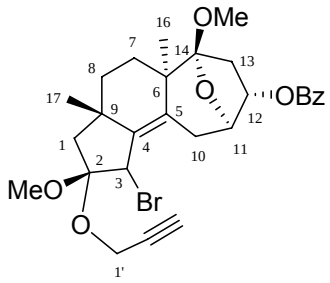
124

A solution of 3% HCl in MeOH (4 mL, prepared by addition of AcCl to MeOH) was added to a solution of **103** (150 mg, 0.378 mmol) and trimethyl orthoformate (4.5 mL) in toluene (25 mL). After 1 h, toluene (8 mL) was added and the reaction mixture was concentrated to a volume of ca. 5 mL by distillation of the solvent at atmospheric pressure. The reaction mixture was concentrated under reduced pressure to give **103** (150 mg, 97%) that was essentially homogeneous by TLC and was used in the next step without further purification. Spectral data for **124** closely matched that reported previously.[47,166]



NOTE: The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left. Spectral assignments are acc ording to the cyathin numbering system as indicated on the structure shown above.

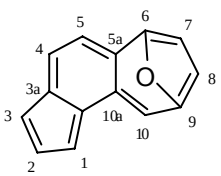
(1R,2R,3aS,5aR,6R,8S,9R)-1-bromo-1,2,3,3a,4,5,5a,6,7,8,9,10-dodecahydro-2,6-dimethoxy-3a,5a-dimethyl-2-(2-propynyloxy)-6,9-epoxycyclohept[e]inden-8-ol benzoate



125

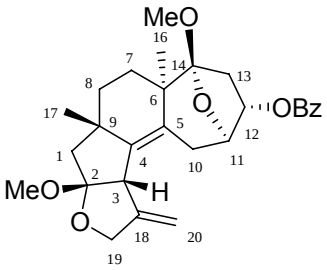
A solution of *N*-bromosuccinimide (recrystallized from benzene; 90 mg, 0.51 mmol) in CH_2Cl_2 (9 mL) was added to a stirred solution of the above crude **124** (150 mg) and distilled propargyl alcohol (0.90 mL, 0.86 g, 15 mmol) in CH_2Cl_2 (6 mL) at –78 °C under argon. After 20 min, the reaction mixture was quenched by addition of 10% aq. $Na_2S_2O_3$ and the cooling bath was removed. The mixture was diluted with CH_2Cl_2 and washed with aq. $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated from benzene (15 mL) to give the crude α-bromo acetal **125** (210 mg) that was used immediately without further purification. Spectral data for **125** closely matched that reported previously.[47,166]

^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.2, 140.8, 134.9, 133.1, 130.2, 129.6 (x2), 128.4 (x2), 111.2, 108.1, 80.0, 79.2, 77.8, 74.0, 52.8, 51.0, 50.3, 49.7, 47.4, 45.9, 40.2, 33.0, 32.6, 29.6, 27.4, 27.0, 19.7



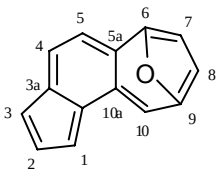
NOTE: The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left. Spectral assignments are according to the cyathin numbering system as indicated on the structure shown above.

(2*R*,3*S*,5*R*,5a*R*,7a*S*,8a*R*,11a*R*)-1,2,3,4,5,5a,6,7,7a,8,8a,10,11,11a-Tetradecahydro-5,8a-dimethoxy-5a,7a-dimethyl-11-methylene-2,5-epoxycyclohept[6,7]indeno[2,1-*b*]furan-3-ol benzoate (126)



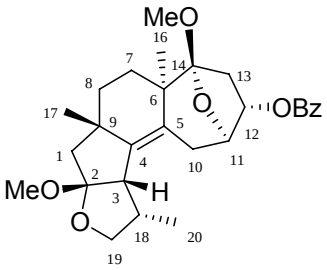
126

Ph_3SnH (200 mg, 0.57 mmol) and AIBN, (12 mg, 0.075 mmol) were added to a solution of the crude **125** (210 mg) in freshly distilled, degassed benzene (25 mL) under argon and the reaction mixture was immersed in an oil bath preheated to 80 °C. After 2 h, the mixture was concentrated and fractionated by MPC (10%–60% ethyl acetate in hexane) to give **126** (102 mg, 66% yield from **103**). Spectral data for **126** closely matched that reported previously.[47,166]



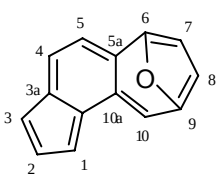
NOTE: The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left. Spectral assignments are according to the cyathin numbering system as indicated on the structure shown above.

(2*R*,3*S*,5*R*,5a*R*,7a*S*,8a*R*,11*S*,11a*S*)-1,2,3,4,5,5a,6,7,7a,8,8a,10,11,11a-Tetradecahydro-5,8a-dimethoxy-5a,7a,11-trimethyl-2,5-epoxycyclohept[6,7]indeno[2,1-*b*]furan-3-ol benzoate (127)



127

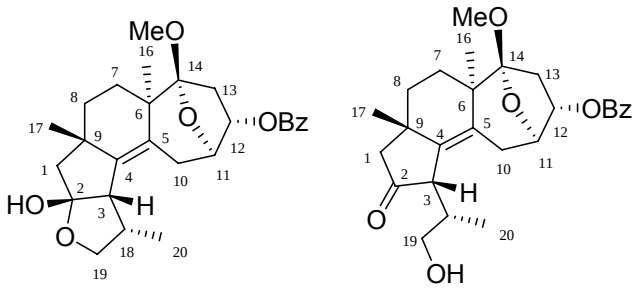
A suspension of 5% Pd/C (75 mg) and **126** (102 mg, 0.215 mmol) in ethyl acetate (15 mL) was stirred under H_2 (3 bar). After 2 days, the mixture was filtered and the combined filtrate and benzene washings were concentrated and fractionated by FCC (20% ethyl acetate in hexane) to give **127** (85 mg, 84% yield). Spectral data for **127** closely matched that reported previously.[47,166]



NOTE: The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left. Spectral assignments are according to the cyathin numbering system as indicated on the structure shown above.

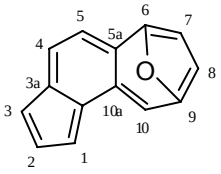
(2*R*,3*S*,5*R*,5a*R*,7a*S*,8a*R*,11*S*,11a*S*)-2,3,4,5,5a,6,7,7a,8,10,11,11a-Dodecahydro-5-methoxy-5a,7a,11-trimethyl-2,5-epoxycyclohept[6,7]indeno[2,1-*b*]furan-3,8a(1*H*)-diol,3-benzoate (128a)

(1*R*,3a*R*,5a*S*,6*S*,8*R*,9*S*)-8-(Benzoyloxy)-3,3a,4,5,5a,6,7,8,9,10-decahydro-1-[(1*R*)-2-hydroxy-1-methylethyl]-6-methoxy-3a,5a-dimethyl-6,9-epoxycyclohept[*e*]inden-2(1*H*)-one (128b)



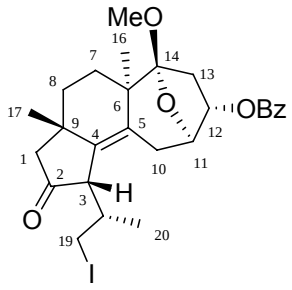
128a, **128b**

Amberlyst (50 mg) was added to a solution of **127** (85 mg, 0.187 mmol) in 7.5% aqueous acetone (2 mL) and the mixture was allowed to stand at room temperature. After 10 h, the mixture was diluted with CH_2Cl_2 and, filtered. The combined filtrate and washings were dried over $NaHCO_3$ and Na_2SO_4, concentrated, and fractionated by FCC (30% ethyl acetate in hexane) to provide recovered **127** (13 mg, 15%) and **128** (60 mg, 73%; 86% based on recovered **127**) as a 1:1.5 mixture of the ring-chain tautomers **128a** and **128b**, respectively. Spectral data for **128** closely matched that reported previously.[47,166]



NOTE: The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left. Spectral assignments are according to the cyathin numbering system as indicated on the structure shown above.

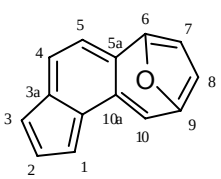
(1*R*,3a*R*,5a*S*,6*S*,8*R*,9*S*)-8-(Benzoyloxy)-3,3a,4,5,5a,6,7,8,9,10-decahydro-1-[(1*R*)-2-iodo-1-methylethyl]-6-methoxy-3a,5a-dimethyl-6,9-epoxycyclohept[*e*]inden-2(1*H*)-one (140)



140

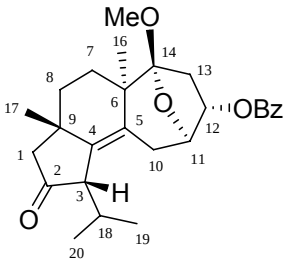
A solution of Ph_2PCl (40 μL, 48 mg, 0.22 mmol) in dry toluene (0.4 mL) was added to a stirred solution of **128** (50 mg, 0.11 mmol) and pyridine (100 μL, 98 mg, 1.24 mmol) in dry toluene (1 mL) at room temperature under argon. After 2 h, the reaction mixture was titrated with a solution of iodine (21 mg, 0.083 mmol) in toluene (1 mL) to a yellow end point. After 1 h, the reaction mixture was concentrated and the residue was fractionated by FCC (10% ethyl acetate in hexane) to give the iodide **140** (43 mg, 70%).

^{1}H NMR (500 MHz $CDCl_3$) δ: 7.5~8.1 (5H, Ar-H), 5.06 (1H, d, *J* = 7 Hz, HC-12), 4.51 (1H, d, *J* = 4 Hz, HC-11), 3.58 (1H, dd, *J* = 9, 9 Hz, HC-19), 3.45 (3H, s, H3C-15), 3.40 (1H, br s, HC-3), 3.29 (1H, dd, *J* = 6.5, 9 Hz, HC-19), 2.68 (1H, m, HC-10), 2.48 (1H, m, HC-18), 2.42 (1H, dd, *J* = 7.5, 15 Hz, HC-10), 2.25 (1H, d, *J* = 16 Hz, HC-1), 2.19 (1H, d, *J* = 16 Hz, HC-1), 2.15 (1H, d, *J* = 15 Hz, HC-13), 2.12 (1H, d, *J* = 15 Hz, HC-13), 1.50~1.90 (4H, m, H_2C-7, 8), 1.29 (3H, s, H_3C-17), 1.12 (3H, s, H_3C-16), 0.91 (3H, d, J = 7 Hz, H_3C-20).



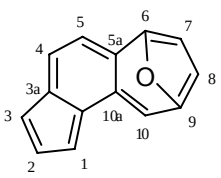
NOTE: The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left. Spectral assignments are according to the cyathin numbering system as indicated on the structure shown above.

(1*R*,3a*R*,5a*S*,6*S*,8*R*,9*S*)-8-(Benzoyloxy)-3,3a,4,5,5a,6,7,8,9,10-decahydro-6-methoxy-3a,5a-dimethyl-1-(1-methylethyl)-6,9-epoxycyclohept[*e*]inden-2(1*H*)-one (141)



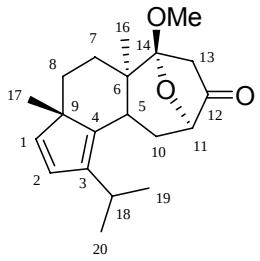
141

A suspension of $BaCO_3$ (ca. 12 mg), Pd black (18 mg), and the iodide **140** (43 mg, 0.076 mmol) in C_6H_6 (5 mL) was stirred under H_2 (1 atm, 1 std atm = 101.325 kPa). After 7 h, the mixture was filtered through Celite and the combined filtrate and washings were concentrated to give **141** (28 mg, 84%). ($[\alpha]_D^{27}$ = -10; *c* = 2.0, CH_2Cl_2) Spectral data for **141** closely matched that reported previously.[47,166]



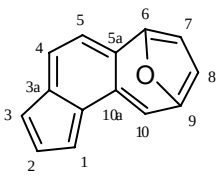
NOTE: The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left. Spectral assignments are according to the cyathin numbering system as indicated on the structure shown above.

(3a*R*,5a*S*,6*S*,9*S*,10a*S*)-4,5,5a,6,7,9,10,10a-Octahydro-6-methoxy-3a,5a-dimethyl-1-(1-methylethyl)-6,9-epoxycyclohept[*e*]inden-8(3a*H*)-one (142)



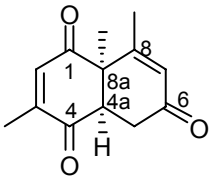
142

To a mixture of triethylamine (0.42 mL, 3 mmol), palladium acetate (4 mg, 0.02 mmol), and triphenylphosphine (10 mg, 0.04 mmol) in DMF (2 mL) was added 99% formic acid (0.075 mL, 2 mmol). This solution (0.16 mL) was added to the triflate **371** (16 mg, 0.034 mmol), and the reaction mixture was stirred at 60 ^{o}C under argon. After 1 h, the mixture was diluted with brine and extracted with ether. The combined organic layers were washed twice with brine, dried over Na_2SO_4, concentrated, and fractionated by FCC to give **142** (8 mg, 75%). ($[\alpha]_D^{27}$ = -70; *c* = 0.9, CH_2Cl_2) Spectral data for **142** closely matched that reported previously.[47,166]



NOTE: The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left. Spectral assignments are according to the cyathin numbering system as indicated on the structure shown above.

(4a*R*,8a*R*),4a,5-Dihydro-3,8,8a-trimethyl-,1,4,6(8a*H*)-naphthalenetrione (297)



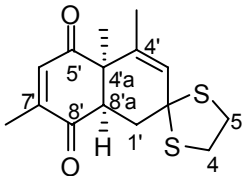
297

Trifluoroacetic acid (0.1 mL) was added to a stirred solution of **108** (2.8 g; ca 95% purity) in MeOH (2 mL) and CH_2Cl_2 (18 mL). After 2 h, toluene (5 mL) was added and the mixture was concentrated to give crude **297** that was purified by FCC (50% ethyl acetate in hexane) to give **297** (1.3 g, 81% from **106**). ($[\alpha]_D^{27}$ = -48; *c* = 1.0 CH_2Cl_2; 93%ee). Spectral data for **297** closely matched that reported previously for racemic material.[46]

Determination of ee of **(-)-297**

The ee of **(-)-297** was determined by ^1H NMR analysis (0.1-0.2 M in $CDCl_3$) in the presence of (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol (6-10 equiv) by integration of the peaks at δ 1.97 (1H, d, *J* = 7 Hz, H_3C-3, **(-)-297**) and δ 1.96 (1H, d, *J* = 7 Hz, H_3C-3, **(+)-297**). Ratios > 30:1 were confirmed by comparison of the minor peak to the ^{13}C satellite (0.55% assumed) of the major peak.

(4a'*R*,8a'*R*)-4',4a',7'-Trimethyl-1'*H*-spiro[[1,3]dithiolane-2,2'-naphthalene]-5',8'(4a'*H*,8a'*H*)-dione (322)



322

p-Toluenesulfonic acid monohydrate (200 mg, 1.05 mmol) was added to a stirred solution of **308** (300 mg, 1.37 mmol) and ethanedithiol (150 mg, 1.60 mmol) in acetic acid (3 mL). After stirring at room temperature overnight, ethyl acetate (20 mL) was added and the mixture was washed with saturated aq. sodium bicarbonate solution (×2), dried over sodium sulfate, and concentrated to give crude **322** that was fractionated by FCC (20% ethyl acetate in hexane) to give **322** (356 mg, 88%). ($[\alpha]_D^{27}$ = -210; *c* = 1.0, CH_2Cl_2).

IR (KBr) ν_{max} (cm^{-1}): 1681, 1627.

^{1}H NMR (500 MHz $CDCl_3$) δ: 6.48 (1H, s, HC-6'), 5.73 (1H, s, HC-3'), 3.18~3.39 (4H, , H_2C-4,H_2C-5), 2.34 (1H, dd, *J* = 2, 12 Hz, HC-1'), 2.28 (1H, dd, *J* = 12, 12 Hz, HC-1'), 1.98 (3H, s, H_3CC-7'), 1.90 (3H, s, H_3CC-4'), 1.38 (3H, s, H_3CC-4a').

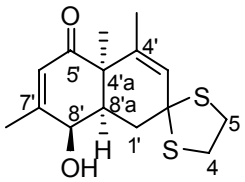
^{13}C NMR (125 MHz, $CDCl_3$) δ: 201.6 (s, C-8'), 200.7 (s, C-5'), 148.1 (s, C-7'), 137.0 (s, C-4'), 136.6 (d, C-6'), 129.4 (d, C-3'), 64.6 (s, C-2), 57.0 (d, C-8'a), 52.0 (s, C-4'a), 44.7 (t, C-1'), 40.9 (t, C-4/5), 40.0 (t, C-4/5), 24.6 (q, CH_3C-4'a), 21.1 (q, CH_3C-4'), 16.3 (q, CH_3C-7')

LRMS (EI), *m/z* (relative intensity): 294 ($[M]^+$, 54), 266 (87), 233 (27), 201

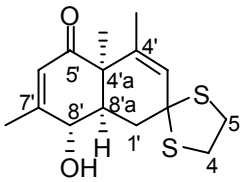
(20), 198 (30), 170 (48), 138 (96), 96 (100).

HRMS *m/z* calcd. for $C_{15}H_{18}O_2S_2$: 294.0748; found: 294.0744 (EI).

(4a'*R*,8'*R*,8a'*R*)-8'-Hydroxy-4',4a',7'-trimethyl-8',8a'-dihydro-1'*H*-spiro[[1,3]dithiolane-2,2'-naphthalen]-5'(4a'*H*)-one (323) and (4a'*R*,8'*S*,8a'*R*)-8'-Hydroxy-4',4a',7'-trimethyl-8',8a'-dihydro-1'*H*-spiro[[1,3]dithiolane-2,2'-naphthalen]-5'(4a'*H*)-one (324)



323



324

$NaBH_4$ (170 mg, 4.47 mmol) was added to a solution of **322** (400 mg, 1.36 mmol) in 1:1 CH_2Cl_2–MeOH (100 mL) at –78 °C. After stirring at –78 °C for 5 h, acetic acid (2 mL) was added and the reaction mixture was allowed to warm to room temperature. Concentration from toluene (×2) provided the crude alcohol that was fractionated by FCC (50% ethyl acetate in hexane) to give a 10:1 mixture of **323** and **324**, respectively, (343 mg, 86%). ($[\alpha]_D^{27}$ = -8; *c* = 0.3, CH_2Cl_2)

IR (KBr) ν_{max} (cm^{-1}): 3441, 1661.

^{1}H NMR (500 MHz $CDCl_3$) δ for **323**: 5.76 (1H, s, HC-6'), 5.73 (1H, s, HC-3'), 4.91 (1H, m, HC-8'), 3.22~3.42 (4H, m, H_2C-4/5), 2.55 (1H, m, HC-1'), 2.40 (1H, ddd, *J* = 2, 5.5, 13 Hz, HC-8'a), 2.02 (3H, s, H_3CC-7'), 2.01 (3H, s, H_3CC-4'), 1.96 (1H, dd, *J* = 13, 13 Hz, HC-1'), 1.34 (3H, s,

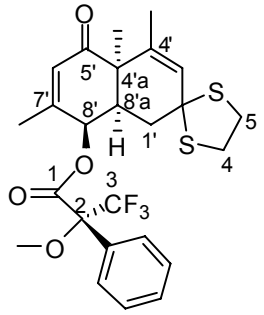
H_3CC-4'a).

^{13}C NMR (125 MHz, $CDCl_3$) δ for **323**: 201.1 (s, C-5'), 158.8 (s, C-7'), 139.1 (s, C-4'), 129.0 (d, C-3'), 125.8 (d, C-6'), 69.2 (d, C-8'), 65.6 (s, C-2), 50.2 (s, C-4'a), 49.2 (d, C-8'a), 40.6 (t, C-4/5), 40.0 (t, C-4/5), 37.9 (t, C-1'), 22.0 (q, CH_3C-4'), 20.5 (q, CH_3C-4'a), 20.1 (q, CH_3C-7').

LRMS (EI), *m/z* (relative intensity): 296 ($[M]^+$, 40), 198 (51), 170 (25), 165 (26), 138 (100), 123 (36), 106 (57), 98 (97).

HRMS *m/z* calcd. For $C_{15}H_{20}O_2S_2$: 296.0905; found: 296.0909 (EI).

(4a'*R*,8'*R*,8a'*R*)-4',4a',7'-Trimethyl-5'-oxo-4a',5',8',8a'-tetrahydro-1'*H*-spiro[[1,3]dithiolane-2,2'-naphthalene]-8'-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (325)



325

Oxalyl chloride (720 μL, 8.21 mmol) was added to a solution of (R)-(+)-MTPA (400 mg, 1.71 mmol) and DMF (113 mg, 1.55 mmol) in hexane (40 mL) at room temperature. A white precipitate formed immediately. After 0.5 h the mixture was filtered and concentrated (water aspirator). A solution of a 10:1 mixture of **323** and **324** (200 mg, 0.67 mmol),

Et_3N (0.83 mL, 0.60 g, 6.0 mmol), and DMAP (117 mg, 0.96 mmol) in $CHCl_3$ (15 mL) was added to the residue. After 10 min, TLC of the mixture revealed complete conversion into the diasteromeric Mosher's esters. 1M HCl was added and the reaction mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were concentrated and fractionated by FCC (20% ethyl acetate in hexane) to give the titled ester (283 mg, 91%). ($[\alpha]_D^{27}$ = -71; *c* = 2.0, CH_2Cl_2)

IR (KBr) ν_{max} (cm^{-1}): 2926, 1751, 1676, 1440, 1252, 1172, 1011.

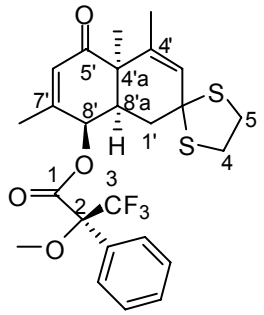
^{1}H NMR (500 MHz $CDCl_3$) δ : 7.51 (2H, Ar-H), 7.36~7.38 (3H, Ar-H), 6.18 (1H, d, *J* = 5 Hz, HC-8'), 5.77 (1H, s, HC-6'), 5.63 (1H, s, HC-3'), 3.51 (3H, s, OMe), 3.16~3.33 (3H, , HC-4, HC-5), 2.90 (1H, ddd, *J* = 5, 9, 11.5 Hz, HC-4 / HC-5), 2.58 (1H, ddd, *J* = 2, 5.5, 13 Hz, HC-8'a), 2.19 (1H, m, HC-1'), 1.93 (1H, m, HC-1'), 1.93 (3H, s, H_3CC-4'), 1.80 (3H, s, H_3CC-7'), 1.35 (3H, s, H_3CC-4'a).

^{13}C NMR (125 MHz, $CDCl_3$) δ : 200.0 (s, C-5), 166.4 (s, C-16), 153.6 (s, C-3), 138.7 (s, C-7), 132.0 (s, Ar-C), 130.3 (d, Ar-C), 129.1 (d, Ar-C), 129.1 (d, Ar-C), 128.9 (d, C-8), 127.9 (d, Ar-C), 127.9 (d, Ar-C), 127.5 (d, C-4), 124.5 (q, C-18), 85.8 (s, C-17), 74.4 (d, C-2), 65.0 (s, C-9), 56.0 (q, O-Me), 50.1 (s, C-6), 46.3 (d, C-1), 40.8 (t, C-14 / C-15), 39.7 (t, C-14 / C-15), 38.4 (t, C-10), 22.0 (q, C-13), 20.5 (q, C-12), 20.1 (q, C-11).

LRMS (EI), *m/z* (relative intensity): 512 ($[M]^+$, 9), 218 (6), 198 (34), 189 (100), 170 (12), 138 (28), 106 (20).

HRMS *m/z* calcd. for $C_{25}H_{27}F_3O_4S_2$: 512.1303; found: 512.1318 (EI).

(4a'*R*,8'*R*,8a'*R*)-4',4a',7'-Trimethyl-5'-oxo-4a',5',8',8a'-tetrahydro-1'*H*-spiro[[1,3]dithiolane-2,2'-naphthalene]-8'-yl) (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (326)



326

Oxalyl chloride (54 μL, 0.62 mmol) was added to a solution of (*S*)-(+)-MTPA (30 mg, 0.12 mmol) and DMF (9 μL, 0.12 mmol) in hexane (0.5 mL) at room temperature. A white precipitate formed immediately. After 0.5 h the mixture was filtered and concentrated (water aspirator). A solution of a 10:1 mixture of **323** and **324** (6 mg, 0.02 mmol), Et_3N (30 μL, 22 mg, 0.21 mmol), and DMAP (35 mg, 0.29 mmol) in $CHCl_3$ (0.5 mL) was added to the residue. After 10 min, TLC of the mixture revealed complete conversion into the diasteromeric Mosher's esters. 1M HCl was added and the reaction mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were concentrated and fractionated by FCC (20% ethyl acetate in hexane) to give the titled ester (8.5 mg, 90%).

IR (KBr) ν_{max} (cm^{-1}): 2926, 2856, 1751, 1676, 1445, 1236, 1183, 1022.

^{1}H NMR (500 MHz $CDCl_3$) δ : 7.54 (2H, Ar-H), 7.33~7.37 (3H, Ar-H), 6.30 (1H, d, *J* = 5 Hz, HC-8'), 5.75 (1H, s, HC-6'), 5.66 (1H, s, HC-3'), 3.56 (3H, s, OMe), 3.21~3.32 (3H, m, HC-4, HC-5), 2.93 (1H, m, HC-4 / HC-5), 2.54 (1H, ddd, *J* = 2, 5.5, 12.5 Hz, HC-8'a), 2.37 (1H, m, HC-1'), 2.00 (1H, dd, *J* = 12.5, 12.5 Hz, HC-1'), 1.94 (3H, s, H_3CC-4'), 1.70 (3H, s, H_3CC-7'), 1.36

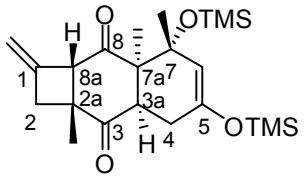
(3H, s, H_3CC-4'a).

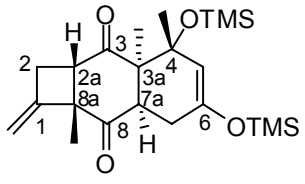
^{13}C NMR (125 MHz, $CDCl_3$) δ: 199.9 (s, C-5'), 166.6 (s, C-1), 153.9 (s, C-7'), 138.8 (s, C-4'), 132.4 (s, Ar-C), 130.3 (d, Ar-C), 129.0 (d, Ar-C), 129.0 (d, Ar-C), 128.9 (d, C-3'), 127.8 (d, Ar-C), 127.8 (d, Ar-C), 127.4 (d, C-6'), 123.7 (q, C-3), 85.0 (s, C-2), 73.7 (d, C-8'), 65.1 (s, C-2), 56.0 (q, O-Me), 50.1 (s, C-4'a), 46.8 (d, C-8'a), 40.7 (t, C-4 / C-5), 39.8 (t, C-4 / C-5), 38.6 (t, C-1'), 22.0 (q, CH_3C-4'), 20.5 (q, CH_3C-4'a), 19.8 (q, CH_3C-7').

LRMS (EI), *m/z* (relative intensity): 512 ($[M]^+$, 15), 198 (57), 189 (100), 170 (21), 138 (46), 106 (34).

HRMS *m/z* calcd. for $C_{25}H_{27}F_3O_4S_2$: 512.1303; found: 512.1318 (EI).

(2a*R*,3a*R*,7a*R*,8a*S*)-1,2,2a,3a,4,7,7a,8a-Octahydro-2a,7,7a-trimethyl-1-methylene-5,7-bis[(trimethylsilyl)oxy]-cyclobuta[*b*]naphthalene-3,8-dione (327a)
(2a*R*,3a*R*,7a*R*,8a*S*)-1,2,2a,3a,4,7,7a,8a-Octahydro-3a,4,8a-trimethyl-1-methylene-4,6-bis[(trimethylsilyl)oxy]-cyclobuta[*b*]naphthalene-3,8-dione (327b)



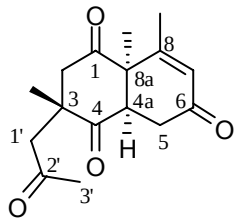


327a **327b**

A solution of **108** (20.0 g, 52.6 mmol) and excess allene (150 mL) in dry

THF (180 mL) was irradiated with a 1200 W mercury vapor lamp in a Pyrex vacuum-jacketed water-cooled immersion well while argon was bubbled through the solution. The entire apparatus was fitted with a dry ice condenser and was immersed in a dry ice–acetone bath that maintained an internal temperature of ca. –50 °C. After 12 h, the bath was removed and the excess allene was recovered (and was reused) by passing the argon effluent through a dry ice condenser and the remaining reaction mixture was concentrated to afford the crude photoadducts as oil (22 g). With similar experiments, a total of 75 g of **108** was converted to 88 g of **327**. The ^{1}H NMR spectrum of the crude products indicated the presence of a 3:1 mixture **327a**, and **327b**, respectively, and closely matched that reported previously.[50]

(3*R*,4a*R*,8a*R*)-3-(2-Oxopropyl)-2,3,4a,8a-tetrahydro-3,8,8a-trimethyl-1,4,6(5*H*)-naphthalenetrione (330)



330

A solution of mercury perchlorate (8.0 g, 20 mmol) in water (450 mL) was added to a stirred solution of a 3:1 mixture of **110** and **109** (10.0 g, 38.7 mol) in acetone (150 mL). The reaction mixture was stirred at room temperature in the dark. After three days, the mixture was concentrated and **330** precipitated as a white solid. The mixture was filtered and the filtrate was extracted with CH_2Cl_2 (3x100 mL). The combined organic layers were concentrated and the residue was combined with the white precipitate.

Trituration with diethyl ether and then acetone gave **330** (5.3 g, 71% based on **110**). ($[\alpha]_D^{27}$ = -3.7; *c* = 1.3, CH_2Cl_2)

IR (KBr) ν_{max} (cm^{-1}): 1709, 1673, 1618.

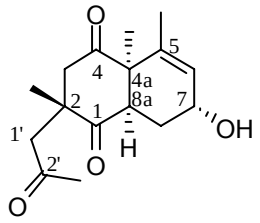
^{1}H NMR (500 MHz $CDCl_3$) δ: 5.77 (1H, s, HC-7), 3.77 (1H, dd, *J* = 2.5, 5 Hz, HC-4a), 3.38 (1H, d, *J* = 15.5 Hz, HC-1'), 3.20 (1H, d, *J* = 18.5 Hz, HC-2), 3.12 (1H, dd, *J* = 2.5, 17.5 Hz, HC-5), 2.54 (1H, d, *J* = 18.5 Hz, HC-2), 2.51 (1H, dd, *J* = 5, 7.5 Hz, HC-5), 2.37 (1H, d, *J* = 15.5 Hz, HC-1'), 2.09 (3H, s, H_3C-3'), 1.89 (3H, s, H_3CC-8), 1.58 (3H, s, H_3CC-8a), 0.93 (3H, s, H_3CC-3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.0 (s, C-4), 209.4 (s, C-1), 207.0 (s, C-2'), 195.5 (s, C-6), 158.9 (s, C-8), 128.5 (d, C-7), 53.9 (t, C-1'), 52.5 (s, C-8a), 51.8 (d, C-4a), 48.8 (t, C-2), 43.9 (s, C-3), 33.3 (t, C-5), 30.3 (q, C-3'), 25.3 (q, H_3CC-8/8a), 24.7 (q, H_3CC-8/8a), 21.0 (q, H_3CC-3).

LRMS (EI), *m/z* (relative intensity): 276 ($[M]^+$, 13), 218 (43), 190 (10), 151 (13), 123 (100), 79 (19).

HRMS *m/z* calcd. for $C_{16}H_{20}O_4$: 276.1362; found: 276.1366 (EI).

(2*R*,4a*R*,7*R*,8a*R*)-7-hydroxy-2,4a,5-Trimethyl-2-(2-oxopropyl)-2,3,8,8a-tetrahydronaphthalene-1,4(4aH,7H)-dione (331)



331

0.1 M aq. NaOH was added dropwise to a stirred solution of crude **340** (5.4 g) in THF (50 mL). After addition of ca. 1 equivalent (14 mL, 14 mmol) a color change from redish to yellow was noted (pH = 9). The reaction mixture was neutralized to pH = 7 by addition of AcOH and then was concentrated. Fractionation of the residue by FCC (40% ethyl acetate in hexane) gave **331** (3.3 g, 82% from **339**). ($[\alpha]_D^{27}$ = +30; *c* = 0.9, CH_2Cl_2)

IR (KBr) ν_{max} (cm^{-1}): 3473, 1697, 1672, 1617.

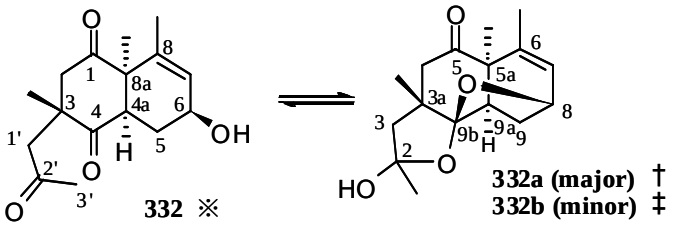
^{1}H NMR (500 MHz $CDCl_3$) δ: 5.45 (1H, s, HC-6), 4.38 (1H, m, HC-7), 3.27 (1H, dd, *J* = 4, 4Hz, HC-8a), 3.21 (1H, d, *J* = 15Hz, HC-1'), 3.17 (1H, d, *J* = 18.5Hz, HC-3), 2.65 (1H, ddd, *J* = 4, 6, 13Hz, HC-8), 2.44 (1H, d, *J* = 18.5Hz, HC-3), 2.29 (1H, d, *J* = 15Hz, HC-11), 2.10 (3H, s, CH_3C-3'), 1.69 (3H, t, *J* = 1.5Hz, H_3C-C5), 1.64 (1H, ddd, *J* = 4, 9, 13Hz, HC-8), 1.49 (3H, s, CH_3C-4a), 0.97 (3H, s, CH_3C-2).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 212.4, 211.0, 206.9, 137.8, 128.7, 64.0, 53.6, 52.8, 52.0, 48.4, 45.1, 30.3, 28.9, 25.5, 25.4, 20.4.

LRMS (EI), *m/z* (relative intensity): 278 ($[M]^+$, 19), 260 (13), 220 (68), 202 (50), 177 (29), 151 (11), 138 (16), 123 (100), 109 (39), 91 (20).

HRMS *m/z* calcd. for $C_{20}H_{22}O_4$: 278.1518; found: 278.1516 (EI).

(2*R*,4a*R*,7*S*,8a*R*)-7-Hydroxy-2,4a,5-trimethyl-2-(2-oxopropyl)-2,3,8,8a-tetrahydronaphthalene-1,4(4a*H*,7*H*)-dione (332)



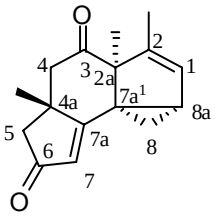
DIBAL-H reduction of **328** as described for the preparation of **339** but quenching with water instead of MeOH gave **332** after fractionation by FCC (30% ethyl acetate in hexane).

^{1}H NMR (500 MHz $CDCl_3$) δ : 5.92† (1H, d, *J* = 6 Hz, HC-7), 5.90‡ (1H, d, *J* = 6 Hz, HC-7), 5.54∗ (1H, m, HC-6), 4.45‡ (1H, dd, *J* = 6, 6 Hz, HC-8), 4.43† (1H, dd, *J* = 6, 6 Hz, HC-8), 4.0∗ (1H, m, HC-7), 3.41∗ (1H, dd, *J* = 4, 4 Hz, HC-9a), 3.10∗ (1H, d, *J* = 15 Hz, HC-1'), 3.08∗ (1H, d, *J* = 18.5 Hz, HC-3), 2.79† (1H, d, *J* = 5 Hz, HC-9a), 2.55∗ (1H, d, *J* = 18.5 Hz, HC-3), 2.55† (1H, d, *J* = 14 Hz, HC-4), 2.47† (1H, d, *J* = 14 Hz, HC-4), 2.41∗ (1H, m, HC-8), 2.32∗ (1H, d, *J* = 15 Hz, HC-1'), 2.30† (1H, m, HC-9), 2.12∗ (1H, ddd, *J* = 4, 7.5, 7.5 Hz, HC-8), 2.08∗ (3H, s, H_3C-3'), 2.01† (1H, d, *J* = 13.5 Hz, HC-3), 1.92† (1H, d, *J* = 13.5 Hz, HC-3), 1.88† (1H, m, HC-9), 1.61∗ (3H, d, *J* = 1.5 Hz, H_3CC-5), 1.54† (3H, s, H_3CC-5a), 1.49‡ (3H, d, J = 1.5 Hz, H_3CC-5), 1.47† (3H, d, *J* = 1.5 Hz, H_3CC-5), 1.40‡ (3H, s, H_3CC-5a), 1.31∗ (3H, s, H_3CC-4a), 1.30‡ (3H, s, H_3CC-2), 1.18† (3H, s, H_3CC-2), 1.16‡ (3H, s, H_3CC-3a), 1.13† (3H, s, H_3CC-3a), 0.98∗ (3H, s, H_3CC-2).

^{13}C NMR (125 MHz, $CDCl_3$) δ : 216.7∗ (s, C-1), 212.4†‡ (s, C-5), 210.7∗ (s, C-4), 206.8∗ (s, C-2'), 138.6† (s, C-6), 138.4‡ (s, C-6), 135.9∗ (s, C-5), 129.5† (d, C-7), 129.3‡ (d, C-7), 129.0∗ (d, C-6), 115.4‡ (s, C-9b), 114.6† (s,

C-9b), 102.5‡ (s, C-2), 101.4† (s, C-2), 72.9‡ (d, C-8), 72.4† (d, C-8), 62.5∗ (d, C-7), 54.6∗ (s, C-4a), 54.1‡ (s, C-4a), 54.0∗ (t, C-1'), 53.1‡ (d, C-8), 52.8† (s, C-5a), 52.4† (d, C-9a), 51.3‡ (t, C-4), 50.6∗ (d, C-8a), 49.8† (t, C-4), 49.7∗ (t, C-3), 49.1‡ (t, C-3), 47.7† (t, C-3), 47.0† (s, C-3a), 46.2‡ (s, C-3a), 45.6∗ (s, C-2), 31.4‡ (t, C-7), 31.1† (t, C-7), 30.48∗ (q, C-3'), 30.46† (q, CH_3C-5a), 29.7‡ (q, CH_3C-5a), 27.1∗ (t, C-8), 25.55∗ (q, CH_3C-5a), 25.52‡ (q, CH_3C-2), 25.1† (q, CH_3C-2), 24.4∗ (q, CH_3C-2), 20.38∗ (q, CH_3C-6), 20.35‡ (q, CH_3C-2), 20.2† (q, CH_3C-2), 18.20‡ (q, CH_3C-6), 18.16† (q, CH_3C-6).

(2a*S*,4a*R*,7a^1*S*,8a*S*)-2,2a,4a-Trimethyl-4a,5,8,8a-tetrahydrocyclopropa [*j*]-as-indacene-3,6(2a*H*,4*H*)-dione (335)



335

To a solution of **336** (20 mg, 0.068 mmol) in THF (5 mL) was added a solution of aq. KOH (1 M;1 mL, 1 mmol) in MeOH (5 mL). The mixture was heated under reflux for 45 min, and after cooling, was neutralized by addition of citric acid. The reaction mixture was concentrated to remove THF and MeOH and then extracted with DCM. The combined organic layers were concentrated and fractionated by FCC (30% ethyl acetate in hexane) to give **335** (12 mg, 75 %).

IR (KBr) ν_{max} (cm^{-1}): 2963, 1705, 1610, 1455, 1270, 1216.

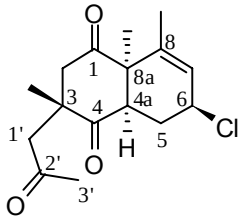
^{1}H NMR (500 MHz $CDCl_3$) δ : 5.79 (1H, s, HC-7), 5.72 (1H, m, HC-1), 2.81 (1H, d, *J* = 4 Hz, HC-5), 2.57 (1H, d, *J* = 4 Hz, HC-5), 2.42 (2H, s, H_2C-4), 2.05 (1H, m, HC-8a), 1.89 (3H, s, CH3C-2), 1.45 (1H, dd, *J* = 4.5, 7.5 Hz, HC-8), 1.29 (3H, s, CH_3C-8a), 1.21 (3H, s, CH_3C-4a), 0.62 (1H, dd, *J* = 4, 4.5 Hz, HC-8).

^{13}C NMR (125 MHz, $CDCl_3$) δ : 211.3, 206.5, 185.0, 142.6, 129.3, 125.1, 63.0, 51.3, 50.5, 45.5, 37.1, 34.6, 27.3, 22.1, 21.5, 15.2.

LRMS (EI), *m/z* (relative intensity): 242 ($[M]^+$, 34), 227 (50), 213 (41), 199 (100), 185 (83), 172 (36), 157 (58), 130 (61).

HRMS *m/z* calcd. for $C_{16}H_{18}O_2$: 242.1307; found: 242.1307 (EI).

(2*R*,4a*R*,7*S*,8a*R*)-7-Chloro-2,4a,5-trimethyl-2-(2-oxopropyl)-2,3,8,8a-tetrahydronaphthalene-1,4(4a*H*,7*H*)-dione (336)



336

DIBAL-H reduction of **328** as described for the preparation of **339** but quenching with 6 M aq. HCl instead of MeOH gave **336** after fractionation by FCC (30% ethyl acetate in hexane).

IR (KBr) ν_{max} (cm^{-1}): 2975, 1711, 1448, 1359, 1210.

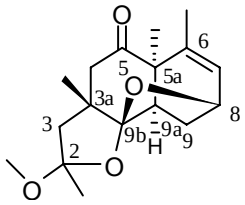
^{1}H NMR (500 MHz $CDCl_3$) δ : 5.51 (1H, s, HC-6), 4.74 (1H, m, HC-7), 3.36 (1H, dd, *J* = 4, 4Hz, HC-8a), 3.26 (1H, d, *J* = 15Hz, HC-1'), 3.20 (1H, d, *J* = 18.5Hz, HC-3), 2.83 (1H, ddd, *J* = 4, 7, 13.5Hz, HC-8), 2.48 (1H, d, *J* = 18.5Hz, HC-3), 2.29 (1H, d, *J* = 15Hz, HC-1'), 2.12 (3H, s, CH_3C-2'), 2.05 (1H, ddd, *J* = 4, 9, 13.5Hz, CH_3C-5), 1.72 (3H, t, *J* = 1.5Hz, HC-8), 1.56 (3H, s, CH_3C-4a), 0.97 (3H, s, CH_3C-2).

^{13}C NMR (125 MHz, $CDCl_3$) δ : 212.0 (s, C1), 210.7 (s, C4), 207.0 (s, C2'), 138.8 (s, C5), 126.9 (d, C6), 72.0 (d, C7), 54.2 (t, C1'), 53.8 (d, C8a), 51.7 (s, C4a), 48.6 (t, C3), 45.1 (s, C2), 30.4 (q, CH_3C-2'), 30.0 (t, C8), 25.7 (q, CH_3C-5), 25.5 (q, CH_3C-2), 20.7 (q, CH_3C-4a).

LRMS (EI), *m/z* (relative intensity): 296 ($[M]^+$, 7), 261 (8), 202 (100), 175 (12), 133 (24), 107 (77), 91 (50).

HRMS *m/z* calcd. for $C_{16}H_{21}O_3Cl$: 296.1179; found: 296.1176 (EI).

(3a*S*,5a*R*,9a*R*)-8,9b-Epoxy-2-methoxy-2,3a,5a,6-tetramethyl-2,3,3a,4,8, 9,9a,9b-octahydronaphtho[1,2-*b*]furan-5(5a*H*)-one (339)

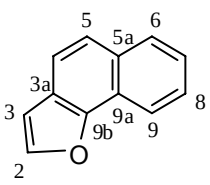


339

To a solution of tetraone **330** (4.0 g, 14.5 mmol) in THF (400 mL) was added 0.5 M 9-BBN (40 mL, 20 mmol) at -10 ^{o}C. The reaction mixture was kept at -10 ^{o}C and was monitored by TLC. After 3 h, **330** was no longer present. The mixture was quenched by addition of MeOH (100 mL) and then concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to give **339** as a colorless oil (4.0 g, 94%).

IR (KBr) ν_{max} (cm^{-1}): 1717.

^{1}H NMR (300 MHz $CDCl_3$) δ : 5.96 (1H, dd, *J* = 1.5, 5.5 Hz, HC-7), 4.47 (1H, dd, *J* = 5.5, 5.5 Hz, HC-8), 3.22 (3H, s, H_3CO), 2.68 (1H, d, *J* = 4.5 Hz, HC-9a), 2.35 (1H, ddd, *J* = 5, 5.5, 10.5 Hz, HC-9), 2.01 (1H, d, *J* = 13.5 Hz, HC-3), 1.93 (1H, d, *J* = 13.5 Hz, HC-3), 1.92 (1H, d, *J* = 18.5 Hz, HC-4), 1.89 (1H, d, *J* = 18.5 Hz, HC-4), 1.64 (1H, m, HC-9), 1.49 (1H, d, *J* = 1.5 Hz, H_3CC-6), 1.46 (3H, s, H_3CC-5a), 1.20 (3H, s, H_3CC-2), 1.17 (3H, s, H_3CC-3a).



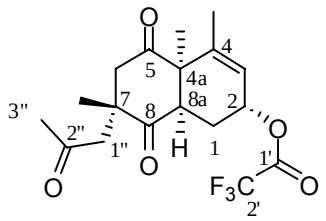
NOTE: The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left.

^{13}C NMR (75 MHz, $CDCl_3$) δ : 212.2 (s, C-5), 138.6 (s, C-6), 129.6 (d, C-7), 114.5 (s, C-9b), 103.8 (s, C-2), 72.2 (d, C-8), 54.7 (s, C-5a), 51.9 (q, H3CO), 50.9 (t, C-4), 49.4 (d, C-9a), 47.4 (t, C-3), 46.6 (s, C-3a), 31.2 (t, C-9), 25.2 (q, H_3CC-6), 24.1 (q, H_3CC-3a), 20.0 (q, H_3CC-5a), 18.2 (q, H_3CC-2).

LRMS (EI), *m/z* (relative intensity): 292 ($[M]^+$, 22), 277 (17), 260 (100), 245 (17), 232 (7), 220 (30), 202 (31), 185 (71).

HRMS *m/z* calcd. for $C_{17}H_{24}O_4$: 292.1675; found: 292.1675 (EI).

(2*R*,4a*R*,7*R*,8a*R*)-4,4a,7-Trimethyl-5,8-dioxo-7-(2-oxopropyl)-1,2,4a,5,6, 7,8,8a-octahydronaphthalen-2-yl 2,2,2-trifluoroacetate (340)



340

To **339** (4.0 g, 13.7 mmol) was added a solution of TFA (3.35 mL, 4.96 g, 43.5 mmol) in DCM (600 mL) at room temperature. After 3 h, the reaction mixture was concentrated to give **340** (5.4 g) as yellow oil, which was used for the next step without further purification.

IR (KBr) ν_{max} (cm^{-1}): 1783, 1711.

^{1}H NMR (500 MHz $CDCl_3$) δ : 5.68 (1H, m, HC-2), 5.41 (1H, brs, HC-3),

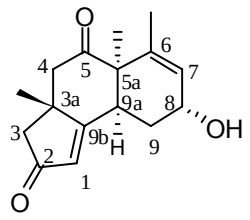
3.46 (1H, d, *J* = 4 Hz, HC-8a), 3.31 (1H, d, *J* = 15 Hz, HC-1'), 3.23 (1H, d, *J* = 18.5 Hz, HC-6), 2.78 (1H, ddd, *J* = 4, 6.5, 12 Hz, HC-1), 2.51 (1H, d, *J* = 18.5 Hz, HC-6), 2.31 (1H, d, *J* = 15 Hz, HC-1"), 2.13 (3H, s, H_3C-3"), 1.77 (3H, d, *J* = 1.5 Hz, CH_3C-4), 1.56 (3H, s, CH_3C-4a), 0.98 (3H, s, CH_3C-7).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 212.0, 210, 207.5, 157.5, 142.4, 129.8, 121.6, 72.6, 53.9, 52.5, 51.7, 48.5, 44.8, 30.3, 25.7, 25.6, 24.3, 20.8.

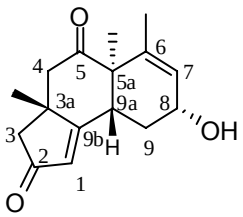
LRMS (EI), *m/z* (relative intensity): 374 ($[M]^+$, 6), 261 (7), 202 (100), 133 (11), 107 (72).

HRMS *m/z* calcd. for $C_{18}H_{21}O_5F_3$: 374.1341; found: 374.1345 (EI).

(3a*R*,5a*R*,8*R*,9a*S*)-3a,4,5a,8,9,9a-Hexahydro-8-hydroxy-3a,5a,6-trimethyl-2*H*-benz[*e*]indene-2,5(3*H*)-dione (341)
(3a*R*,5a*R*,8*R*,9a*R*)-3a,4,5a,8,9,9a-Hexahydro-8-hydroxy-3a,5a,6-trimethyl-2*H*-benz[*e*]indene-2,5(3*H*)-dione (342)



341



342

To a stirred solution of **331** (3.3 g, 13 mmol) in THF (600 mL) and MeOH (600 mL) was added in 1 M aq. KOH (95 mL, 95 mmol). The mixture was heated under reflux for 45 min, and, after cooling, was neutralized by addition of citric acid. The reaction mixture was concentrated to remove the

THF and MeOH and was extracted with DCM. The combined organic layers were fractionated by FCC (70% ethyl acetate in hexane) to give a 1:1 mixture of **341** and **342** (2.73 g, 88%). Pure samples of **341** and **342** were obtained by fractionation of the mixture by FCC (30%-60% ethyl acetate in hexane).

Data for **341**

IR (KBr) ν_{max} (cm^{-1}): 3456, 3383, 1699, 1617.

^{1}H NMR (500 MHz $CDCl_3$) δ: 6.14 (1H, s, HC-1), 5.80 (1H, d, *J* = 5.5 Hz, HC-7), 4.21 (1H, m, HC-8), 3.46 (1H, dd, *J* = 3, 14 Hz, HC-9a), 2.89 (1H, d, *J* = 12.5 Hz, HC-4), 2.53 (1H, d, *J* = 18.0 Hz, HC-3), 2.44 (1H, d, *J* = 12.5 Hz, HC-4), 2.42 (1H, d, *J* = 18.0 Hz, HC-3), 1.90 (1H, ddd, *J* = 3.5, 14, 14 Hz, HC-9), 1.82 (1H, m, HC-9), 1.77 (3H, s, CH_3C-6), 1.38 (3H, s, CH_3C-5a), 1.53 (3H, s, CH_3C-3a).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.5, 206.2, 183.6, 140.7, 131.8, 125.9, 62.7, 54.6, 53.5, 50.1, 48.0, 45.0, 34.6, 28.9, 24.1, 20.5.

LRMS (EI), *m/z* (relative intensity): 260 ($[M]^+$, 74), 245 (51), 217 (13), 203 (24), 177 (44), 146 (11), 123 (35), 109 (100), 84 (39).

HRMS *m/z* calcd. for $C_{16}H_{20}O_3$: 260.1412; found: 260.1410 (EI).

Data for **342**

IR (KBr) ν_{max} (cm^{-1}): 3444, 3433, 3382, 1700, 1694, 1621.

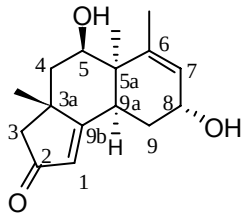
^{1}H NMR (500 MHz $CDCl_3$) 5.99 (1H, d, *J* = 1.5 Hz, HC-1), 5.47 (1H, m, HC-7), 4.41 (1H, m, HC-8), 2.87 (1H, d, *J* = 12.5 Hz, HC-4), 2.86 (1H, ddd, *J* = 1.5, 1.5, 12.5 Hz, HC-9a), 2.47 (1H, s, HC-3), 2.46 (1H, s, HC-3), 2.42 (1H, d, *J* = 12.5 Hz, HC-4), 2.21 (1H, dddd, *J* = 1.5, 1.5, 5.5, 12.5 Hz, HC-9), 1.87 (3H, dd, *J* = 1.5, 1.5 Hz, CH_3C-6), 1.82 (1H, ddd, *J* = 10, 12.5, 12.5 Hz, CH_3C-9), 1.28 (3H, s, CH_3C-5a), 1.26 (3H, s, CH_3C-3a).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.4, 206.6, 183.5, 139.5, 128.8, 127.7, 66.9, 53.8, 52.1, 50.7, 45.0, 42.3, 29.6, 27.2, 19.7, 19.6.

LRMS (EI), *m/z* (relative intensity): 260 ($[M]^+$, 80), 245 (100), 203 (33), 202 (68), 177 (34), 123 (25), 109 (71), 84 (84).

HRMS *m/z* calcd. for $C_{16}H_{20}O_3$: 260.1412; found: 260.1409 (EI).

(3a*S*,5*R*,5a*R*,8*S*,9a*S*)-3,3a,4,5,5a,8,9,9a-Octahydro-5,8-dihydroxy-3a,5a,6-trimethyl-2*H*-benz[*e*]inden-2-one (343)

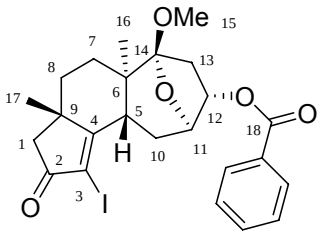


343

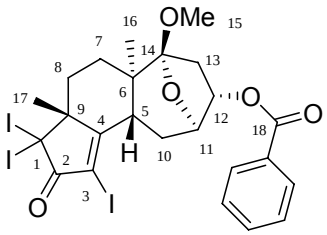
$NaBH_4$ (400 mg, 10.6 mmol) was added to a solution of a 1:1 mixture of **341** and **342** (2.37 g, 9.04 mmol) in 1:1 DCM–MeOH (150 mL) at –78 °C. After standing at –78 °C for 5 h, acetic acid (5 mL) was added with stirring and the reaction mixture was allowed to warm to room temperature.

Concentration from toluene (×2) provided a 1:1 mixture of **343** and **115** (2.16 g, 91%). The crude alcohols were used in the next step without further purification. A pure sample of **343,** obtained by fractionation of the mixture by MPC (50% ethyl acetate in hexane), gave a ^{1}H NMR spectrum that closely matched the previously reported data.[50]

(3a*R*,5a*S*,6*S*,8*R*,9*S*,10a*S*)-3-Iodo-8-(benzoyloxy)-3a,4,5,5a,6,7,8,9,10, 10a-decahydro-6-methoxy-3a,5a-dimethyl-6,9-epoxycyclohept[e]inden -2(3*H*)-one (356) and
(3a*R*,5a*S*,6*S*,8*R*,9*S*,10a*S*)-1,1a,3-Triiodo,8-(benzoyloxy)-3a,4,5,5a,6,7,8, 9,10,10a-decahydro-6-methoxy-3a,5a-dimethyl-6,9-epoxycyclohept[*e*] inden-2(3*H*)-one (358)

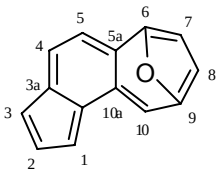


356



358

To a solution of **103** (5 mg, 0.02 mmol), I_2 (8.8 mg, 0.035 mmol) and pyridine (12.5 μL, 12.3 mg, 0.15 mmol) in CCl_4 (12.5 μL) was added $TMSN_3$



NOTE: The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left. Spectral assignments are according to the cyathin numbering system as indicated on the structure shown above.

(30 μL, 26 mg, 0.22 mmol). The reaction mixture was allowed to stand at room temperature for two weeks, then 10% $Na_2S_2O_3$ aq was added, the mixture was extracted with DCM, concentrated and purified with MPC to give **358** (1.7 mg, 26%) and **356** (0.5 mg, 5%).

Data for **356**

^{1}H NMR (500 MHz $CDCl_3$) δ: 7.4~8.1 (5H, Ar-H), 5.26 (1H, d, J = 7.5 Hz, HC-12), 4.54 (1H, brs, HC-11), 3.39 (3H, s, HC-15), 3.11 (1H, , HC-5), 2.92 (1H, ddd, *J* = 3.5, 13.5, 13.5 Hz, HC-10), 2.75 (1H, dd, *J* = 3.5, 13.5 Hz, HC-10), 2.59 (1H, dd, *J* = 7.5, 15 Hz, HC-13), 2.48 (1H, d, *J* = 18.5 Hz, HC-1), 2.37 (1H, d, *J* = 18.5 Hz, HC-1), 2.15 (1H, m, HC-13), 1.5~1.9 (4H, m, H2C-7, H_2C-8), 1.33 (3H, s, H_3C-17), 1.01 (3H, s, H_3C-16).

LRMS (EI), *m/z* (relative intensity): 522 ($[M]^+$, 6), 288 (100), 234 (32), 105 (100).

HRMS *m/z* calcd. for $C_{24}H_{27}IO_5$: 522.0904; found: 522.0909 (EI).

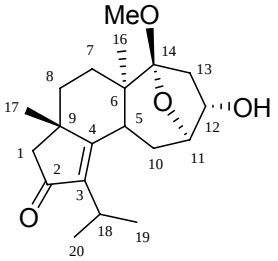
Data for **358**

^{1}H NMR (500 MHz $CDCl_3$) δ: 5.31 (1H, dd, *J* = 5.5, 8 Hz, HC-12), 4.61 (1H, brs, HC-11), 3.43 (3H, s, HC-15), 3.02 (1H, ddd, *J* = 4, 13.5, 13.5 Hz, HC-10), 2.91 (1H, dd, *J* = 4, 13.5 Hz, HC-5), 2.60 (1H, dd, *J* = 7.5, 15.5 Hz, HC-13), 2.22 (1H, m, HC-13), 2.03 (1H, ddd, *J* = 2, 4, 13.5 Hz, HC-10), 1.7~2.0 (4H, m, H_2C-7, 8), 1.44 (3H, s, H_3C-17), 1.07 (3H, s, H_3C-16).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.5 (s, C-2), 181.5 (s, C-4), 166.8 (s, C-18), 133.8 (d, Ar-C), 130.1 (d, Ar-C), 130.1 (d, Ar-C), 129.2 (s, Ar-C),

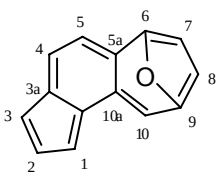
128.9 (d, Ar-C), 128.9 (d, Ar-C), 111.1 (s, C-14), 101.1 (s, C-3), 78.6 (d, C-11), 77.1 (d, C-12), 49.8 (q, C-15), 52.4 (s, C-9), 46.2 (s, C-6), 41.7 (d, C-5), 32.5 (t, C-13), 30.1 (s, C-1), 29.6 (t, C-8), 28.2 (t, C-10), 27.6 (t, C-7), 21.1 (q, C-17), 12.5 (q, C-16).

(3a*R*,5a*S*,6*S*,8*R*,9*S*,10a*S*)-3a,4,5,5a,6,7,8,9,10,10a-Decahydro-8-hydroxy-6-methoxy-3a,5a-dimethyl-1-(1-methylethyl)-6,9-epoxycyclohept[*e*]inden-2(3*H*)-one (370)



370

Aqueous NaOH (1 M, 1.2 mL) was added to a solution of **141** (28 mg, 0.064 mmol) in MeOH (10 mL) and the mixture was heated under reflux. After 10 h, the mixture was diluted with CH_2Cl_2, washed with satd. $NaHCO_3$, dried over Na_2SO_4, concentrated to give **370** (18 mg, 84%), which was homogeneous by ^1H NMR and was used in the next step without further purification. ($[\alpha]_D^{27}$ = -48; *c* = 2.9, CH_2Cl_2)



NOTE: The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left. Spectral assignments are according to the cyathin numbering system as indicated on the structure shown above.

IR (KBr) ν_{max} (cm^{-1}): 3429, 1696, 1616.

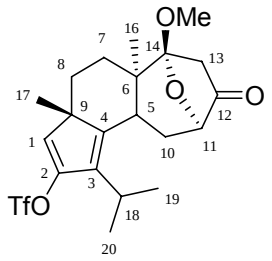
^{1}H NMR (500 MHz $CDCl_3$) δ: 4.28 (1H, m, HC-12), 4.23 (1H, s, HC-11), 3.39 (3H, s, H_3C-15), 2.97 (1H, qq, *J* = 7, 7 Hz, H_3C-18), 2.60 (1H, dd, *J* = 3.5, 13 Hz, HC-5), 2.50 (1H, dd, *J* = 7, 14.5 Hz, HC-13), 2.34 (1H, ddd, *J* = 3.5, 13, 13 Hz, HC-10), 2.22 (1H, d, *J* = 18.5 Hz, HC-1), 2.15 (1H, d, *J* = 18.5 Hz, HC-1), 1.90 (1H, m, HC-13), 1.80 (1H, m, HC-7/8), 1.70 (1H, ddd, *J* = 2, 4, 13 Hz, HC-10), 1.40~1.60 (3H, m, H_2C-7/8), 1.24 (3H, s, H_3C-16/17), 1.22 (3H, d, *J* = 7 Hz, H_3C-19/20), 1.21 (3H, d, J = 7 Hz, H_3C-19/20), 0.99 (3H, s, H_3C-16/17).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.4, 173.3, 143.8, 111.2, 81.8, 75.2, 52.6, 49.2, 45.4, 40.1, 39.2, 36.4, 35.4, 28.3, 27.7, 26.5, 26.1, 20.4, 20.1, 12.1.

LRMS (EI), *m/z* (relative intensity): 334 ($[M]^+$, 14), 307 (10), 204 (100), 189 (40), 176 (21), 162 (22), 149 (15).

HRMS *m/z* calcd. for $C_{20}H_{30}O_4$: 334.2144; found: 334.2137 (EI).

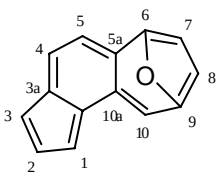
(3a*R*,5a*S*,6*S*,9*S*,10a*S*)-3a,4,5,5a,6,7,8,9,10,10a-Decahydro-6-methoxy-3a,5a-dimethyl-1-(1-methylethyl)-8-oxo-6,9-epoxycyclohept[*e*]inden-2-yl trifluoromethanesulfonate (371)



371

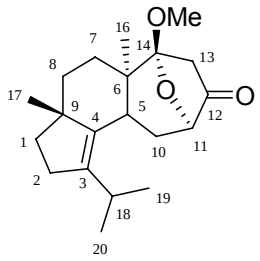
A solution of Tf_2O in CH_2Cl_2 (0.5 M, 0.18 mL, 0.09 mmol) was added to a stirred solution of 2,4,6-tri-*tert*-butylpyrimidine (25 mg, 0.10 mmol) and **102** (16 mg, 0.048 mmol) in CH_2Cl_2 (4 mL) under argon and the mixture was heated under reflux. After 2 h, the mixture was concentrated and the residue taken up in pentane and filtered. The combined filtrate and washings were concentrated and fractionated by FCC (10% ethyl acetate in hexane) to give the enol triflate **371** (16 mg, 72%).

^{1}H NMR (500 MHz $CDCl_3$) δ: 6.12 (1H, s, HC-1), 4.34 (1H, br s, HC-11), 3.42 (3H, s, H_3C-15), 3.06 (1H, qq, *J* = 7 Hz, HC-18), 2.78 (1H, d, *J* = 18.5 Hz, HC-13), 2.57 (1H, d, *J* = 18.5 Hz, HC-13), 2.52 (1H, dd, *J* = 3, 13.5 Hz, HC-5), 2.42 (1H, ddd, *J* = 3, 12, 13.5 Hz, HC-10), 1.93 (1H, ddd, *J* = 3, 3, 12 Hz, HC-10), 1.79 (1H, m, HC-8), 1.54 (1H, m, HC-7), 1.42 (1H, ddd, *J* = 3.5, 13, 13 Hz, HC-8), 1.32 (1H, ddd, *J* = 4, 13, 13 Hz, HC-7), 1.22 (3H, d, *J* = 7 Hz, H_3C-19), 1.16 (3H, d, *J* = 7 Hz, H_3C-20), 1.06 (3H, s, H_3C-17), 0.94 (3H, s, H_3C-16).



NOTE: The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left. Spectral assignments are according to the cyathin numbering system as indicated on the structure shown above.

(3a*R*,5a*S*,6*S*,9*S*,10a*S*)-2,3,3a,4,5,5a,6,7,9,10,10a-decahydro-6-methoxy-3a,5a-dimethyl-1-(1-methylethyl)-6,9-epoxycyclohept[*e*]inden-8(3a*H*)-one (372)

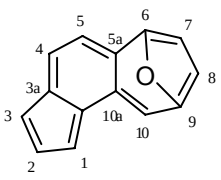


372

A suspension of 10% Pd/C (4 mg) and **142** (8 mg, 0.025 mmol) in MeOH (8 mL) was stirred under H_2 (1 atm, 1 std atm = 101.325 kPa). After 1 h, the mixture was filtered through Celite and the combined filtrate and washings were concentrated to give **372** (7 mg, 88%) ($[\alpha]_D^{27}$ = -58; *c* = 1.7, CH_2Cl_2)

IR (KBr) ν_{max} (cm^{-1}): 1763.

^{1}H NMR (500 MHz $CDCl_3$) δ : 4.29 (1H, s, HC-11), 3.40 (3H, s, H_3C-15), 2.88 (1H, qq, *J* = 7 Hz, HC-18), 2.69 (1H, d, *J* = 19 Hz, HC-13), 2.52 (1H, d, *J* = 19 Hz, HC-13), 2.34 (1H, m, HC-5), 2.20~2.34 (2H, m, H_2C-2), 1.95 (1H, m, HC-10), 1.67 (1H, ddd, *J* = 3.5, 6.5, 12 Hz, HC-10), 1.2~1.65 (6H, m, H_2C-1, 7, 8), 1.07 (3H, s, H_3C-16/17), 1.02 (3H, d, *J* = 7 Hz, H_3C-19/20), 0.97 (3H, s, H_3C-16/17), 0.92 (3H, d, *J* = 7 Hz, H_3C-19/20).



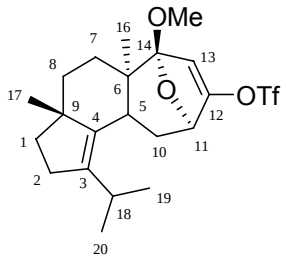
NOTE: The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left. Spectral assignments are according to the cyathin numbering system as indicated on the structure shown above.

^{13}C NMR (125 MHz, $CDCl_3$) δ: 215.2, 141.5, 135.1, 109.4, 80.9, 49.8, 48.2, 44.5, 40.1, 39.3, 37.4, 37.2, 30.0, 29.9, 29.2, 26.7, 24.1, 22.7, 21.6, 12.8.

LRMS (EI), *m/z* (relative intensity): 318 ($[M]^+$, 23), 303 (7), 190 (100), 175 (62), 149 (21), 127 (36), 114 (22), 105 (12).

HRMS *m/z* calcd. for $C_{20}H_{30}O_3$: 318.2195; found: 318.2197 (EI).

(3a*R*,5a*S*,6*S*,9*S*,10a*S*)-2,3,3a,4,5,5a,6,9,10,10a-Octahydro-6-methoxy-3a,5a-dimethyl-1-(1-methylethyl)-6,9-epoxycyclohept[*e*]inden-8-yl-trifluoromethanesulfonate (373)



373

$NaN(TMS)_2$ (1 M in THF, 0.175 mL, 0.175 mmol) was added to a stirred solution of ketone **372** (7 mg, 0.022 mmol) and $PhN(Tf)_2$ (25 mg, 0.07 mmol) in THF (2.5 mL) at –78 °C under argon. After 30 min, the reaction was

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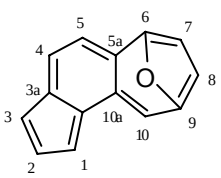
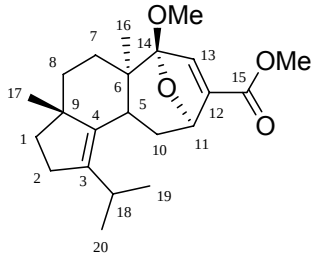


NOTE: The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left. Spectral assignments are according to the cyathin numbering system as indicated on the structure shown above.

quenched by addition of water. The mixture was diluted with ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated, fractionated by MPC (5% ethyl acetate in hexane) to give the enol triflate **373** (8.5 mg, 89%).

^{1}H NMR (500 MHz $CDCl_3$) δ : 6.05 (1H, s, HC-13), 4.73 (1H, m, HC-11), 3.34 (3H, s, H_3C-15), 2.90 (1H, septet, *J* = 7 Hz, HC-18), 2.53 (1H, m, HC-5), 2.20~2.35 (3H, m, H_2C-2, HC-10), 2.03 (1H, m, HC-10), 1.20~1.80 (6H, m, H_2C-1, 7, 8), 1.01 (3H, d, *J* = 7 Hz, H_3C-19/20), 0.98 (3H, s, H_3C-16/17), 0.97 (3H, s, H_3C-16/17), 0.92 (3H, d, *J* = 7 Hz, H_3C-19/20).

(3a*R*,5a*S*,6*S*,9*S*,10a*S*)-methyl-2,3,3a,4,5,5a,6,9,10,10a-Decahydro-6-methoxy-3a,5a-dimethyl-1-(1-methylethyl)-6,9-epoxycyclohept[*e*]-indene-8-carboxylate (374)



374

$Pd(Ph_3P)_4$ (20 mg, 0.018 mmol) and MeOH (0.3 mL) were sequentially added to a stirred solution of the triflate **373** (8.5 mg, 0.019 mmol) and

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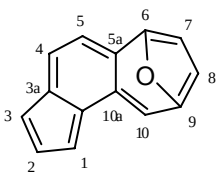


NOTE: The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left. Spectral assignments are according to the cyathin numbering system as indicated on the structure shown above.

i-Pr_2EtN (6 μL, 6 mg, 0.046 mmol) in CO saturated THF (3 mL) at room temperature. The mixture was stirred under CO (1 atm, 1 std atm = 101.325 kPa) for 1 h and then was concentrated and fractionated by MPC (5% ethyl acetate in hexane) to give the ester **374** (4.5 mg, 66%). ($[\alpha]_D^{27}$ = -140; *c* = 1.0, CH_2Cl_2)

IR (KBr) ν_{max} (cm^{-1}): 1721.

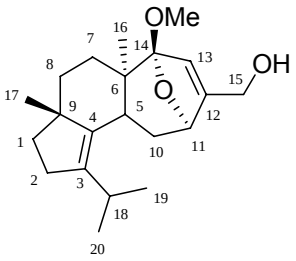
^{1}H NMR (500 MHz $CDCl_3$) δ: 7.00 (1H, s, HC-13), 4.96 (1H, s, HC-11), 3.74 (3H, s, H_3C-22), 3.26 (3H, s, H_3C-15), 2.84 (1H, qq, *J* = 7 Hz, HC-18), 2.10~2.25 (4H, m, H_2C-2, HC-5, 10), 1.70~1.05 (7H, m, H_2C-1, 7, 8, HC-10), 0.93 (3H, d, *J* = 7 Hz, H_3C-19/20), 0.92 (3H, s, H_3C-16/17), 0.85 (3H, s, H_3C-16/17), 0.82 (3H, d, *J* = 7 Hz, H_3C-19/20).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.2, 147.8, 140.3, 136.2, 135.6, 114.7, 79.7, 52.3, 51.7, 48.3, 42.1, 40.2, 39.9, 37.2, 30.7, 28.8, 26.9, 26.5, 24.3, 22.3, 21.4, 12.1.

LRMS (EI), *m/z* (relative intensity): 360 ($[M]^+$, 22), 345 (47), 317 (7), 277 (10), 257 (7), 204 (22), 189 (100), 95 (10), 69 (13).

HRMS *m/z* calcd. for $C_{22}H_{32}O_4$: 360.2301; found: 360.2306 (EI).

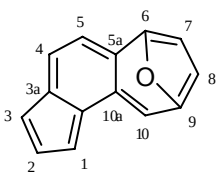
(3a*R*,5a*S*,6*S*,9*S*,10a*S*),2,3,3a,4,5,5a,6,7,8,9,10,10a-Dodecahydro-6-methoxy-3a,5a-dimethyl-1-(1-methylethyl)-6,9-epoxycyclohept[*e*]-indene-8-methanol (Cyathin A_3 methyl acetal) (375)



375

DIBAL-H (1.5 M in toluene, 0.15 mL, 0.225 mmol) was added to a stirred solution of **374** (8 mg, 0.024 mmol) in dry ether (3 mL) under argon at –20 °C. After 30 min, the reaction was quenched by addition of MeOH (1 mL). After 1 h, the mixture was diluted with ether, washed with brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (60% ethyl acetate in hexane) to give **375** (5.8 mg, 74%). ($[\alpha]_D^{27}$ = -150; *c* = 0.8, MeOH) (lit.[3] $[\alpha]_D$ = -154; c=0.24, MeOH)

IR (KBr) ν_{max} (cm^{-1}): 3320.



NOTE: The compound name is according to the ***Chemical Abstracts*** skeleton shown on the left. Spectral assignments are according to the cyathin numbering system as indicated on the structure shown above.

^{1}H NMR (500 MHz $CDCl_3$) δ: 6.06 (1H, s, HC-13), 4.79 (1H, m, HC-11), 4.33 (2H, m, H_2C-15), 3.31 (3H, s, H_3C-21), 2.95 (1H, qq, *J* = 6.5, 6.5 Hz, HC-18), 2.40 (1H, m, HC-5), 2.24 (3H, m, H_2C-2, HC-10), 1.8~1.2 (7H, m, H_2C-1, 7, 8, HC-10), 1.03 (3H, d, *J* = 6.5 Hz, H_3C-19), 1.01 (3H, s, H_3C-16), 0.97 (3H, s, H_3C-17), 0.93 (3H, s, *J* = 6.5 Hz, H_3C-20).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 148.4, 139.4, 136.5, 124.4, 114.3, 78.4, 59.7, 51.1, 48.3, 42.3, 40.2, 40.0, 37.2, 30.3, 28.8, 27.2, 26.5, 24.5, 22.5, 21.3, 12.0.

LRMS (EI), *m/z* (relative intensity): 332 ($[M]^+$, 13), 256 (13), 190 (15), 175 (29), 141 (100), 97 (47), 69 (77).

HRMS *m/z* calcd. for $C_{21}H_{32}O_3$: 332.2352; found: 332.2339 (EI).

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